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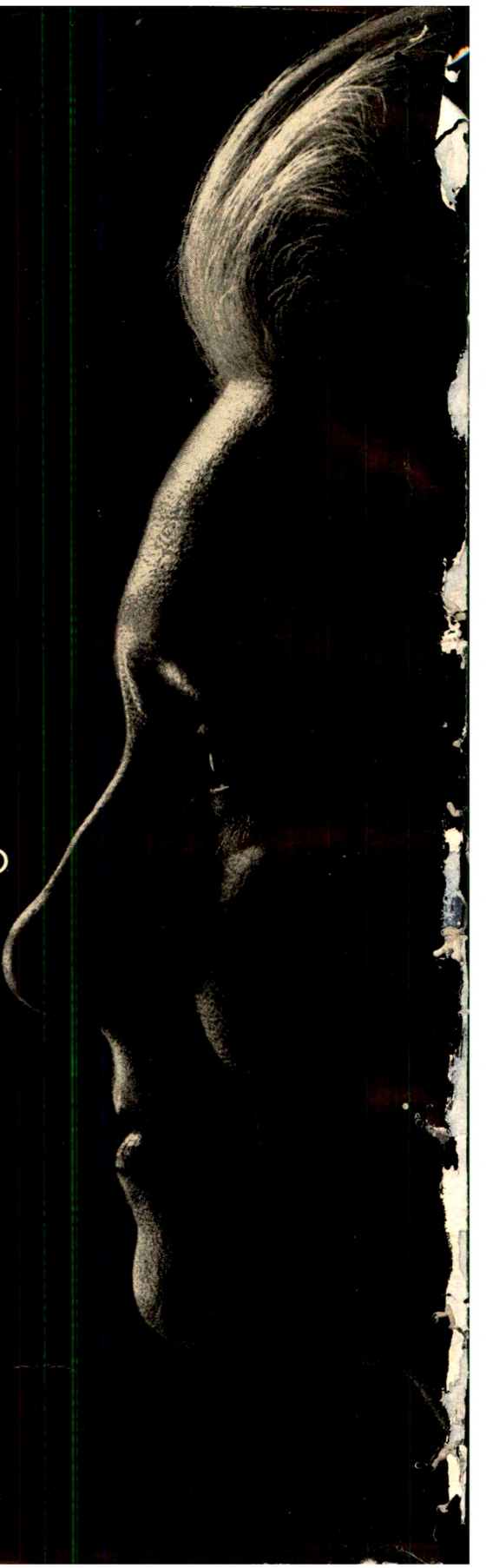
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Isopto Carbachol 3%
controls
diurnal variation
without
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## ERRATUM

The legends for five illustrations in color in "The Corneal Graft," by Thomas E. Moore, Jr., M.D., and Samuel B. Aronson, M.D., which appeared in a special supplement in July, 1971 (72:205, 1971) were incorrect. Readers may wish to clip the correct labels reprinted below and paste them on the appropriate pages.

Page 219:



Fig. 9 (Moore and Aronson). Postoperative morphologic classification. (A) Absent host neovascularization following keratoplasty in keratoconus. (B) Mild host neovascularization following grafting in aphakic bullous keratoplasty. Note superficial vessels in the host cornea at four and 10 o'clock positions. (C) Moderate host neovascularization following grafting in herpes simplex keratitis (3+). Note superficial and deep vessels throughout the host cornea. (D) Moderate host neovascularization following graft for alkali keratitis. Note sequential distribution of neovascularization.

Fig. 11 (Moore and Aronson). Surgery-induced inflammation (early graft reaction). (A) Patient 5, preoperatively demonstrates a large central descemetocele below a partially retracted flap. (B) Postoperative endophthalmitis (photograph taken eight weeks following surgery). (C) Histology of ciliary body demonstrates a low-grade cyclitis. (D) Histology of posterior eye shows perivascular cellular cuffing of a retinal vessel with minimal-to-absent vitreous involvement.

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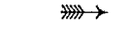


Fig. 10 (Moore and Aronson). A-B. Primary donor failure (early graft reaction). (A) Patient 1, histology of donor cornea demonstrating endothelial stripping (×40). (B) Same patient, demonstrating sub- and intraepithelial edema. C-H. Surgery-induced early graft reaction. (C) Patient 2, graft failure following wound dehiscence, pictured 10 weeks after surgery. (D) Same patient four months after subsequent keratoplasty. (E) Patient 3, descemetocele following wound dehiscence at the time of suture removal. (F) Same patient, demonstrating a subsequently clear graft six months postoperatively. (G) Patient 4, demonstrating wound dehiscence following cutting of the continuous nylon suture (three weeks postoperation). (H) Same patient at six months after surgery with a clear graft. Note the area of inferior scarring.

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Fig. 12 (Moore and Aronson). Suture toxicity (early graft reaction). (A) Patient 6 demonstrates early failure as a result of silk suture toxicity six weeks following surgery. (B) Same patient with subsequent keratoplasty in which 10-0 Ethilon suture was used, demonstrating a clear graft 10 weeks after surgery. (C) Patient 7 demonstrates early graft failure secondary to silk suture toxicity 12 weeks after surgery. (D) same patient demonstrating a clean graft one year after surgery. 10-0 Ethilon suture was used. (E) Patient 8 at four weeks postsurgery demonstrates reaction to 8-0 silk suture, with no reaction to nylon suture. (F) Another patient with penetrating keratoplasty demonstrates reaction to 9-0 virgin silk with relative lack of reaction to nylon. (G) Another patient with keratoconus in whom continuous nylon suture was used. Suture tracts are free of infiltrate. (H) Same patient (higher magnification), demonstrating the lack of infiltrate.

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Fig. 13 (Moore and Aronson). A-F. Microbial toxicity (early graft reaction). G-H. Tissue incompatibility (early graft reaction). (A) Patient 9, demonstrating severe pseudomonas infection. (B) Same patient following inflammatory inactivation with combined corticosteroid Polysporin therapy. (C) Same patient four days after surgery, demonstrating a pseudomonas, suture-tract abscess following penetrating keratoplasty. (D) Same patient 12 weeks after surgery, demonstrating a clear graft. Note area of corneal scarring in the eight o'clock meridian. (E) Patient 10, three weeks postsurgery, demonstrating inflammatory infiltrate and neovascularization around interrupted sutures. The continuous suture is free of reaction. (F) Same patient one week after removal of interrupted suture. Note involution of conjunctival neovascularization. (G) Patient 11, demonstrating graft failure seven months after surgery. (H) Same patient (high magnification). Note that many superficial and deep vessels enter the donor cornea between suture tracts.

The following corrections in text are necessary:

Page 223, left column: line 1, figures 12-E and F; line 5, figures 12-G and H.

Page 224, right column: line 8, figure 9; line 11, figure 9-A, figure 9-B; line 13, figures 11-C and D.

Page 229, right column: line 18, figure 10-A; line 19, figure 10-B.

Page 231, left column: line 5, figure 10-C; right column: lines 9 and 10, figures 10-C and 10-D; line 19, figure 10-E.

Page 232, left column: line 9, figure 10-E; line 13, figure 10-F; line 32, figure 10-G; line 34, figure 10-H; right column: line 6, figure 10-G; line 11, figure 10-H; line 26, figure 11-B; line 31, figure 11-A; next to bottom line, figure 11-B.

Page 233, left column: line 17, figures 11-C and D.

Page 234, left column: line 27, figure 12-A; line 29, figure 12-B; right column: next to bottom line, figure 12-A.

Page 235, left column: line 7, figure 12-B; line 13, figure 12-C; line 15, figure 12-D; line 30, figure 12-C; line 37, figure 12-D; line 44, figure 12-E; right column: line 3, figure 12-E; line 10, figure 12-F; line 17, figures 12-G and H.

Page 236, left column: line 20, figure 13; line 23, figure 13-B; next to bottom line, figure 13-C; right column: line 13, figure 13-D.

Page 239, right column: top line, figure 13-E; line 10, figure 13-F; legend, line 5, figure 10-D.

Page 240, right column: line 18, figure 13-G; line 22, figure 13-H.

Page 249, right column: line 7, figure 10-D.

Page 295, right column: line 13, figure 10-C.

The JOURNAL regrets these errors.



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*Drance, S.M. and Flindall, R. J.; Canad. J. of Ophth. *1*:#4:292-296, Oct. 1966

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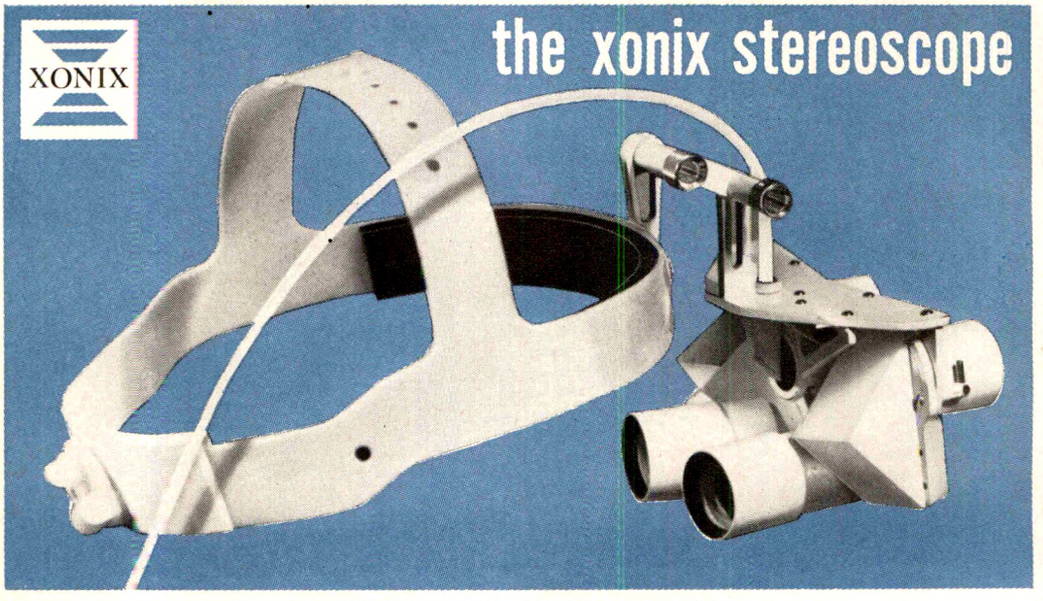
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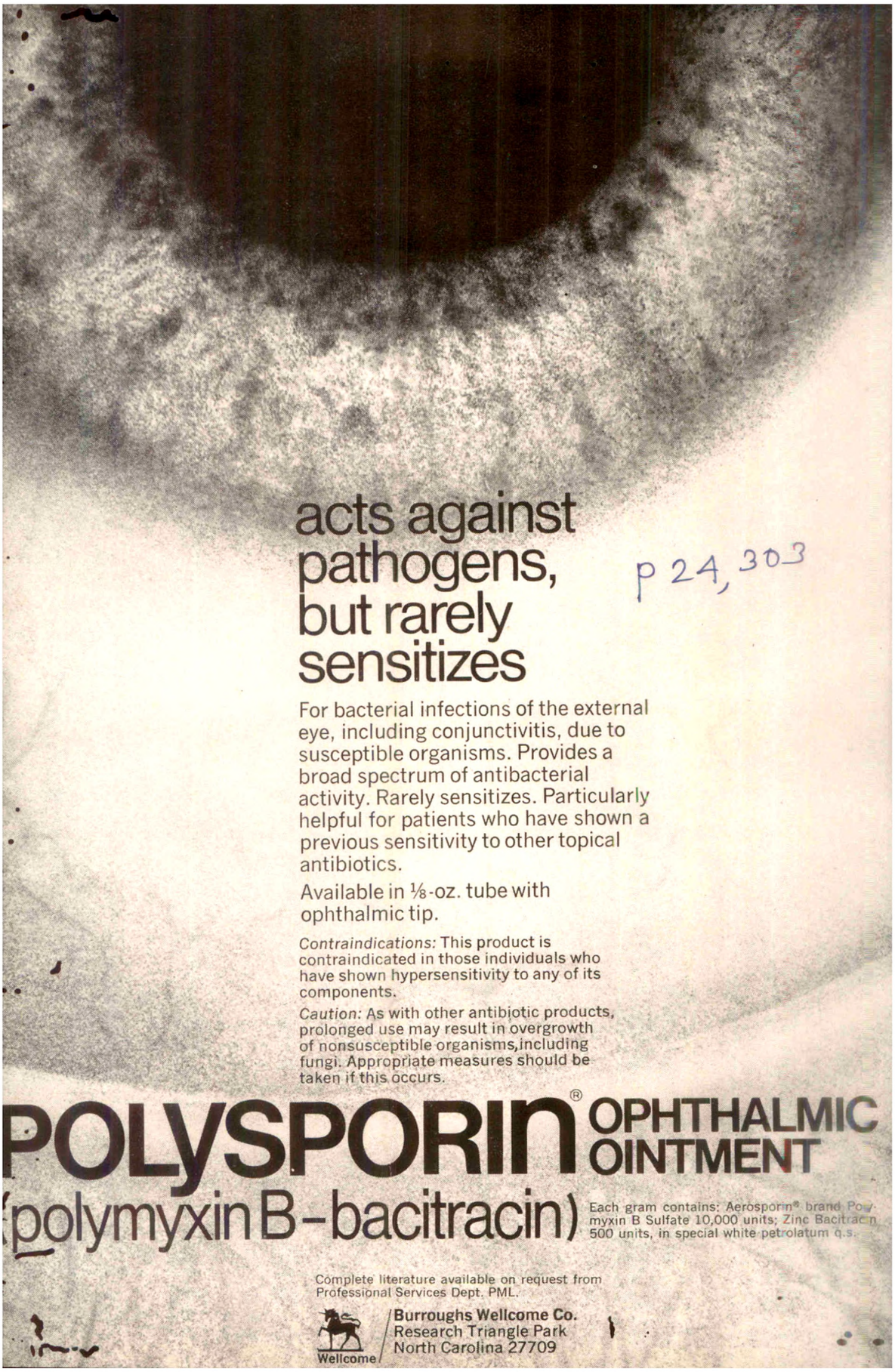
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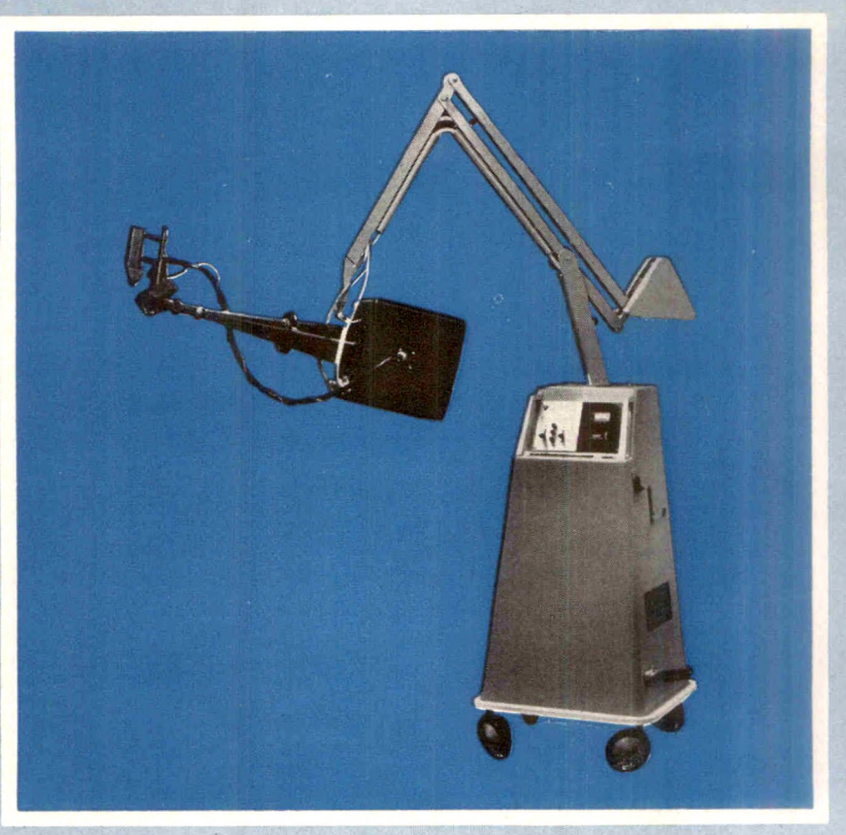
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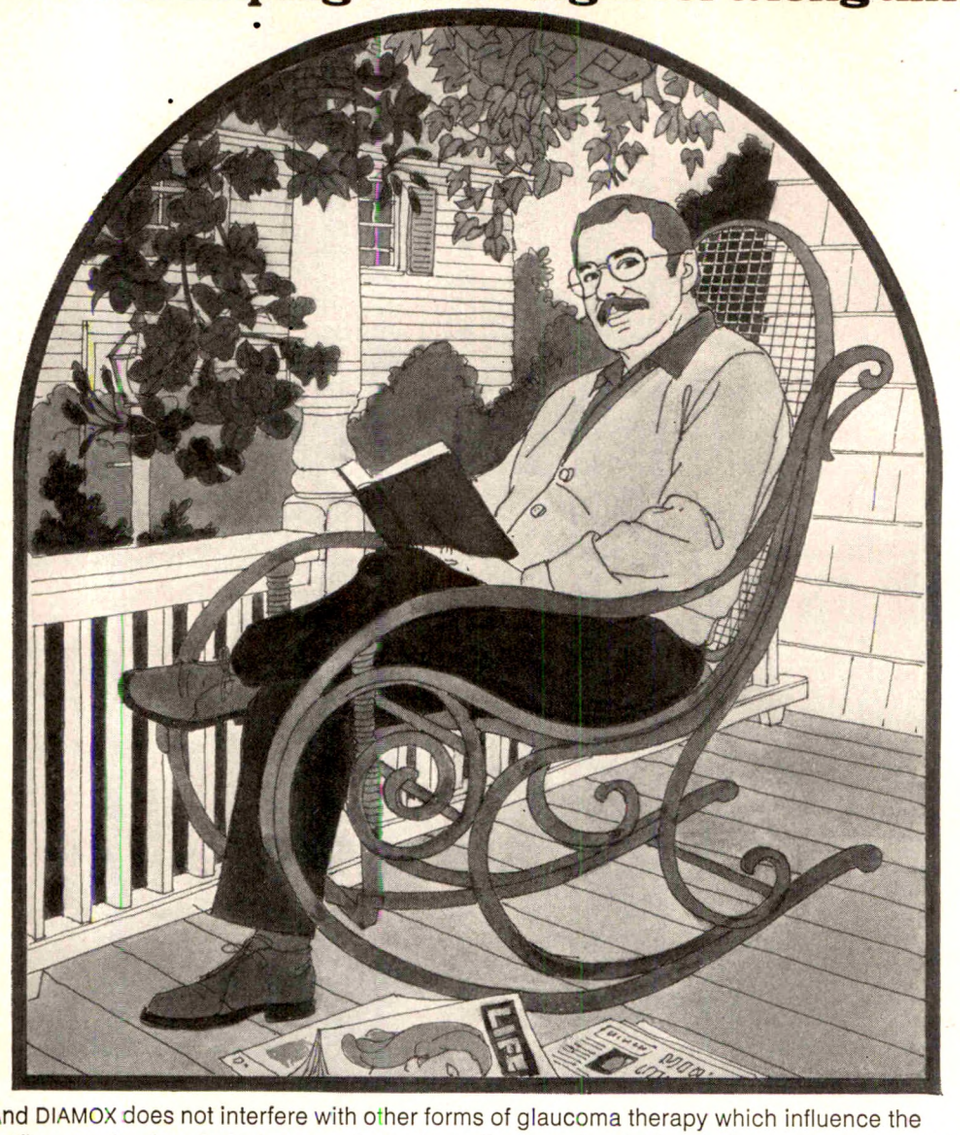
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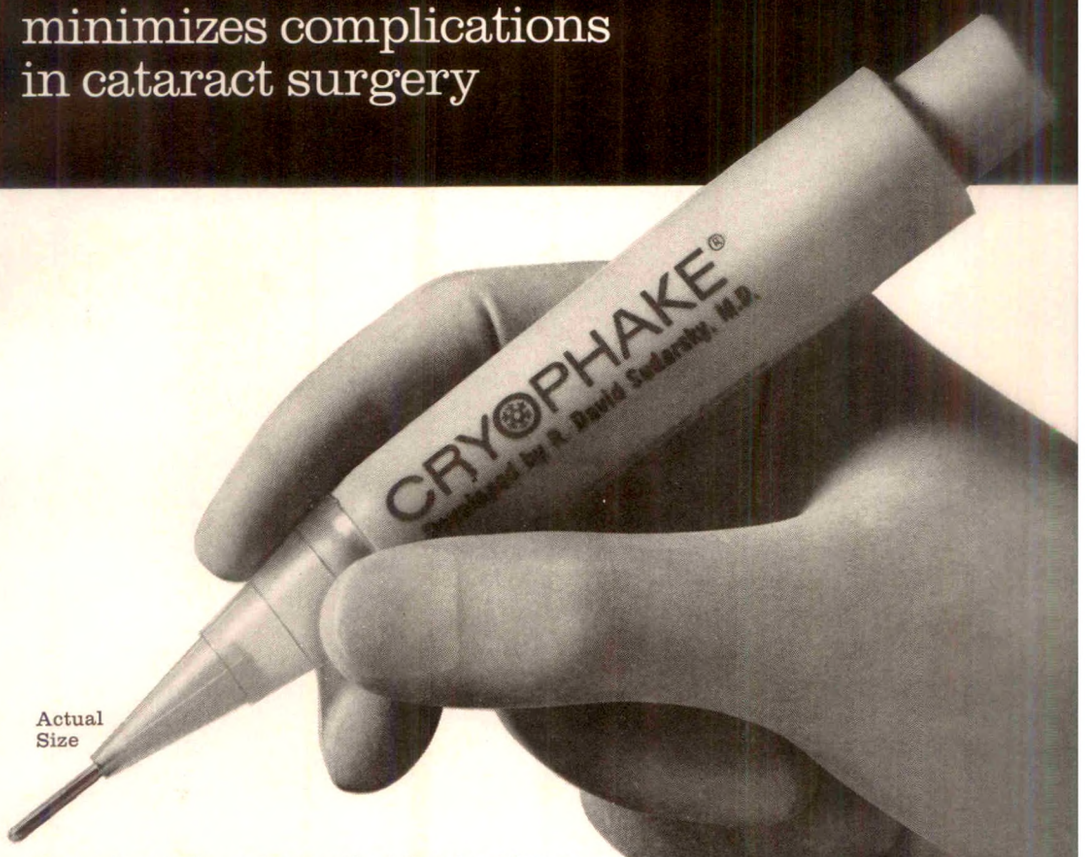
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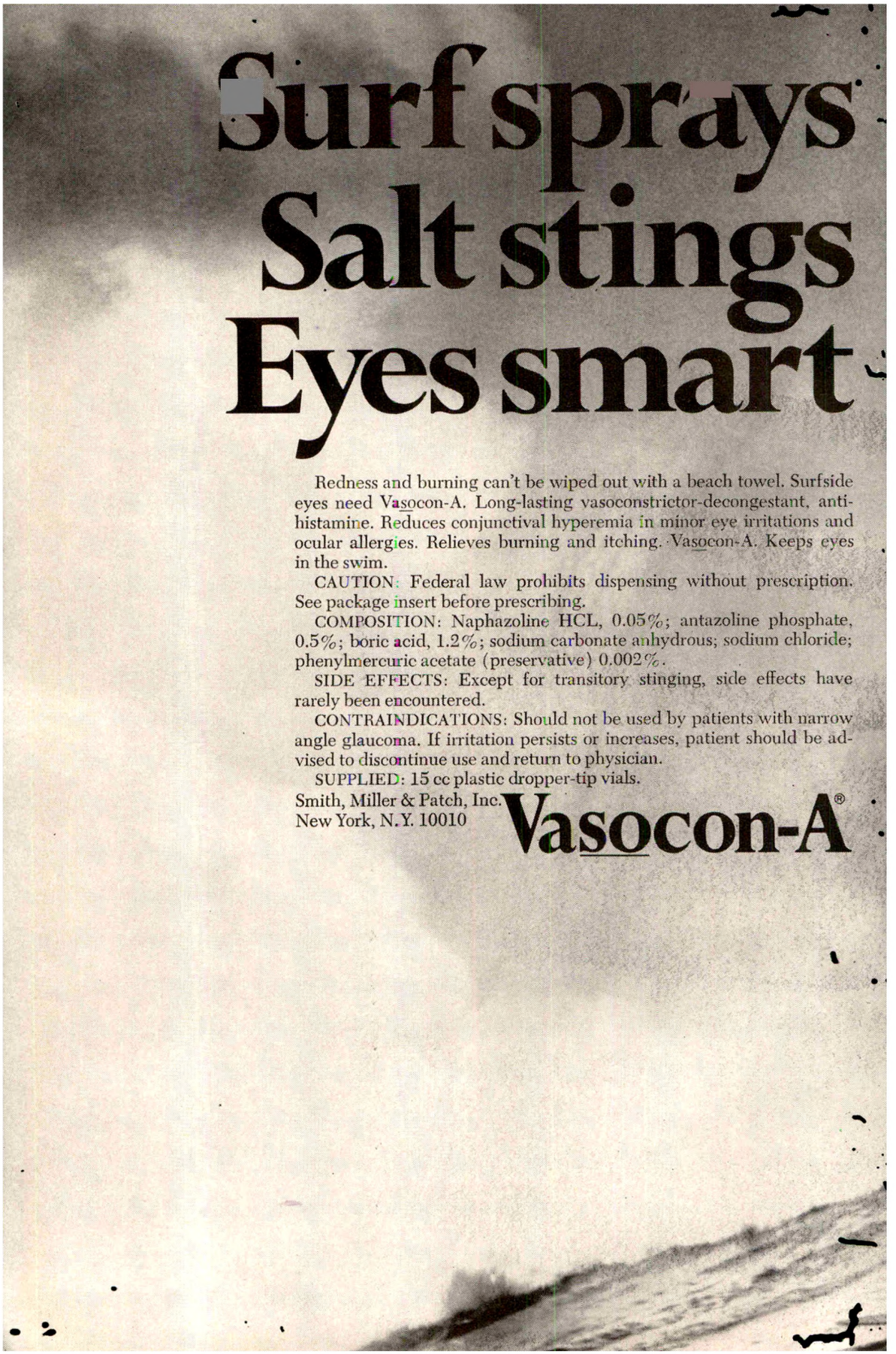
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b. If the spectacle cylinder is *greater* than the corneal cylinder, the residual astigmatism will *not* be reduced, and may actually be increased with ultra-thin lenses.

c. If the corneas are *spherical,* the residual astigmatism *will not be affected* by the use of ultra-thin lenses.

A more complete discussion of these factors appears in my monograph "More About Small, Thin Contact Lenses: Visual Considerations". When it is found that ultra-thin lenses are visually contraindicated, or do not sufficiently reduce the residual astigmatism, we must turn to *astigmatic lenses:*

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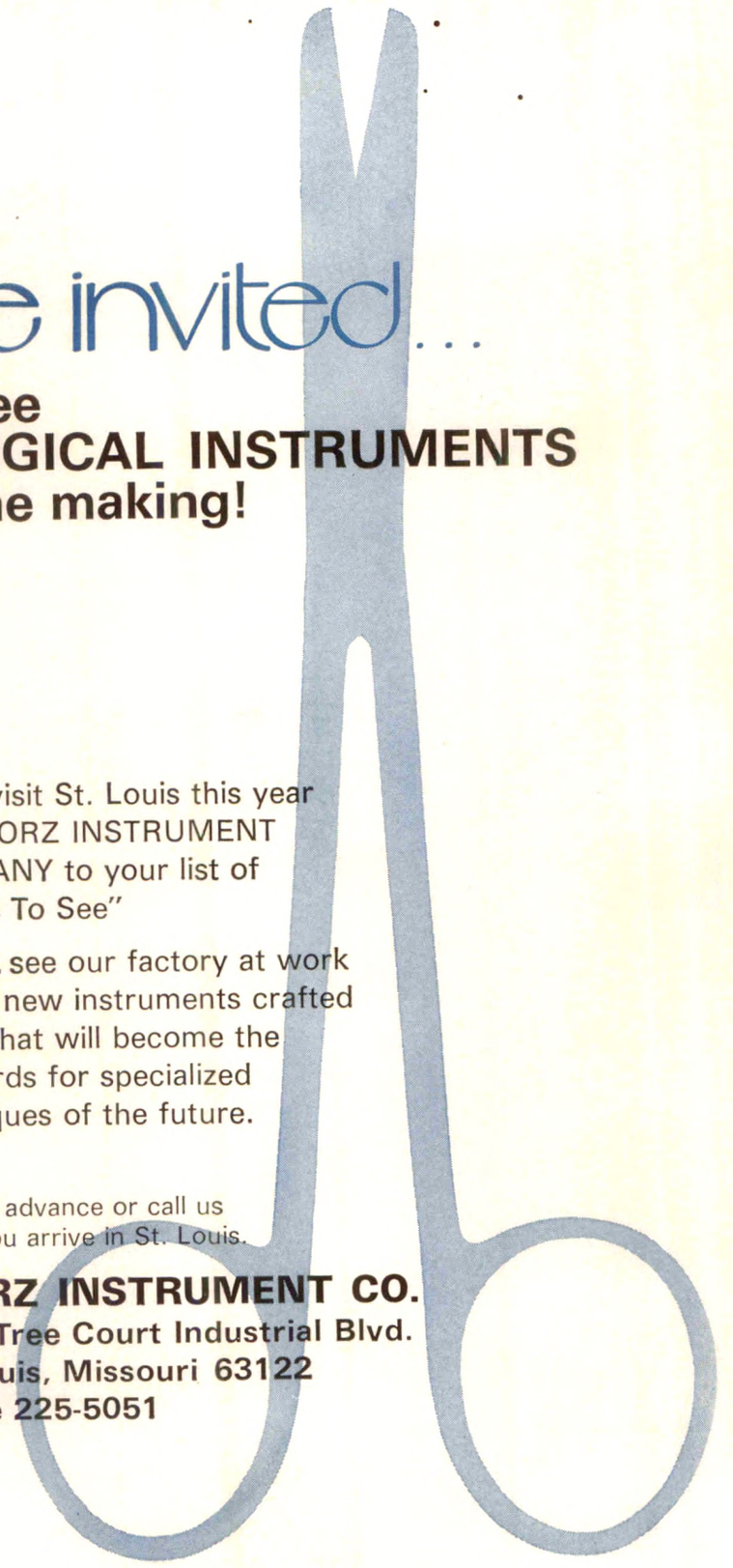
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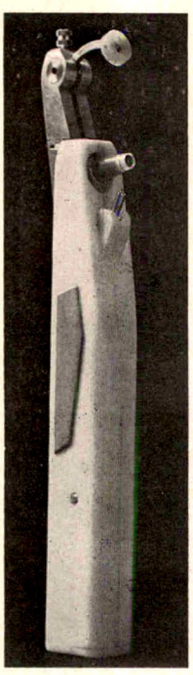


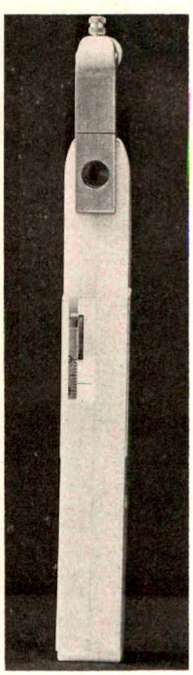
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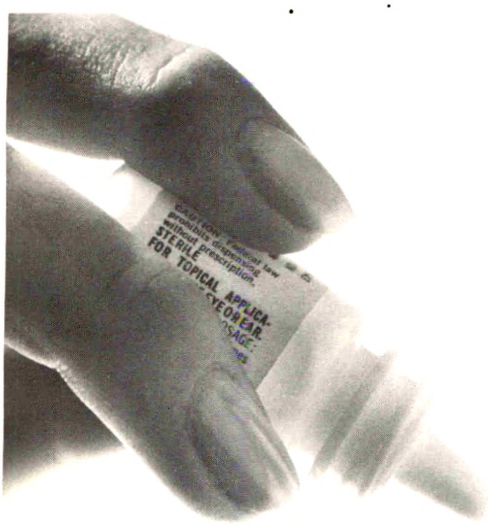
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As with other corticosteroids, increased intraocular tension can follow extended local use (1-2 weeks or more) of dexamethasone sodium phosphate. Since increased intraocular tension can lead to loss of vision, this possibility should be kept in mind and topical administration used only under adequate tonometric supervision, particularly in patients known to have glaucoma, or whose family history includes glaucoma.

In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. Reports in the literature indicate that, rarely, protracted use of topical corticosteroids in the eye may be associated with the development of posterior subcapsular cataracts. Hereditary and degenerative eye diseases in general do not show any response to treatment with these preparations.

Stubborn cases of anterior segment eye disease may require systemic adrenocortical hormone therapy. When the deeper ocular structures are involved, systemic therapy is necessary.

NeoDECADRON: A few individuals may be sensitive to one or more of the components of NeoDECADRON. If any reaction indicating sensitivity is observed, discontinue use. Sensitivity to neomycin may occasionally develop, especially when it is applied to abraded skin. Some reports in the current literature point to an increase in the number of persons sensitive to neomycin.

Use of any antibiotic agent may result in overgrowth of fungi or other organisms not susceptible to the antibiotic, necessitating prompt medical attention for such new infections.

As the safety of topical steroids during pregnancy has not been confirmed, they should not be used for extended periods during pregnancy.

**For more detailed information, consult your MSD Representative or see the Direction Circular. Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa. 19486**

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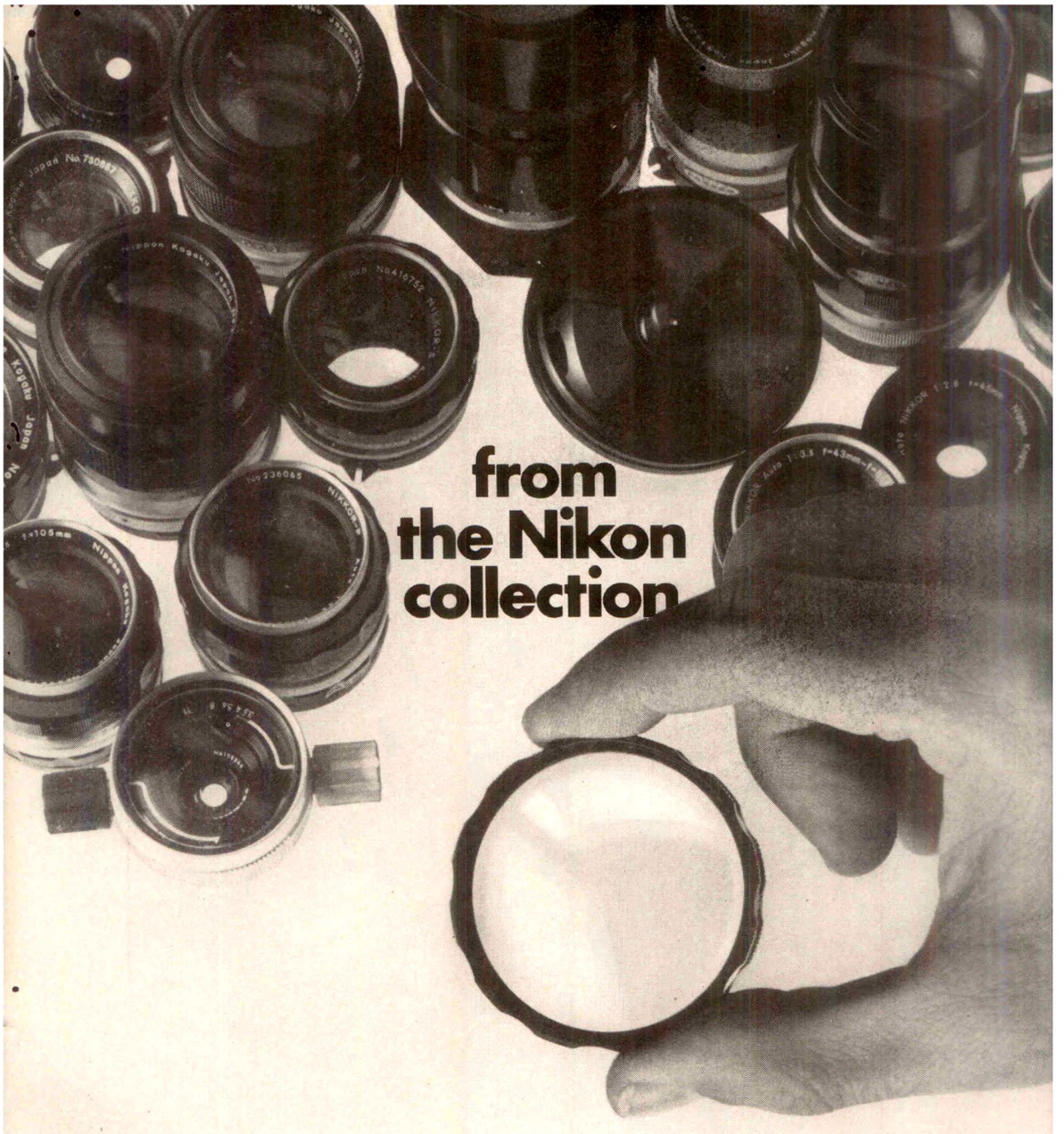
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Nikon Instrument Division, Subsidiary of Ehrenreich Photo-Optical Industries, Inc. Garden City, New York. 11530 (In Canada: Anglophoto, Ltd., Ont.)

**Nikon Aspherical Ophthalmoscopic Lens**

**Composition:**

**Inflamase**

*Prednisolone Sodium Phosphate .....0.125%
(Equivalent to Prednisolone 0.1%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

**Inflamase Forte**

*Prednisolone Sodium Phosphate 1.0%
(Equivalent to Prednisolone 0.8%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

Prednisolone Sodium Phosphate is a water soluble inorganic ester of prednisolone. It is approximately 2,000 times as soluble in water at 25°C. as is hydrocortisone.

*Licensed under patent #3,134,718.

**Indications:** Inflamase and Inflamase Forte ophthalmic solutions may be used effectively in the following conditions of the anterior segment of the eye: superficial keratitis, including punctate epithelial lesions (Thygeson type), phlyctenular keratoconjunctivitis, and Sjogren's keratoconjunctivitis (with systemic steroids); deep keratitis, including interstitial or parenchymatous keratitis, acne rosacea, sclerosing keratitis; herpes zoster opthalmicus (do not use in herpes simplex); non-purulent conjunctivitis, including vernal, allergic, catarrhal; iridocyclitis; acute iritis; recurrent marginal ulceration, whether endogenous or due to atopic or contact allergies, or microbial allergy; corneal injuries, such as aseptic thermal, radiation, or chemical burns and corneal injuries following surgery or the penetration of foreign bodies; lid allergy; and non-purulent blepheritis, including catarrhal and allergic.

Inflamase and Inflamase Forte ophthalmic solutions have their principal effect on the anterior segment of the eye (cornea and the anterior uvea), with acute disorders responding more favorably than chronic disorders. Inflamase Forte 1% solution is recommended for moderate to severe inflammations particularly when rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

**Dosage:** Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops 2 to 4 times daily.

**Contraindications:** Contraindicated in acute herpes simplex, ocular tuberculosis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal diseases of the eye. Purulent conjunctivitis, purulent blepharitis, and infectious conditions are contraindications to the use of steroids.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

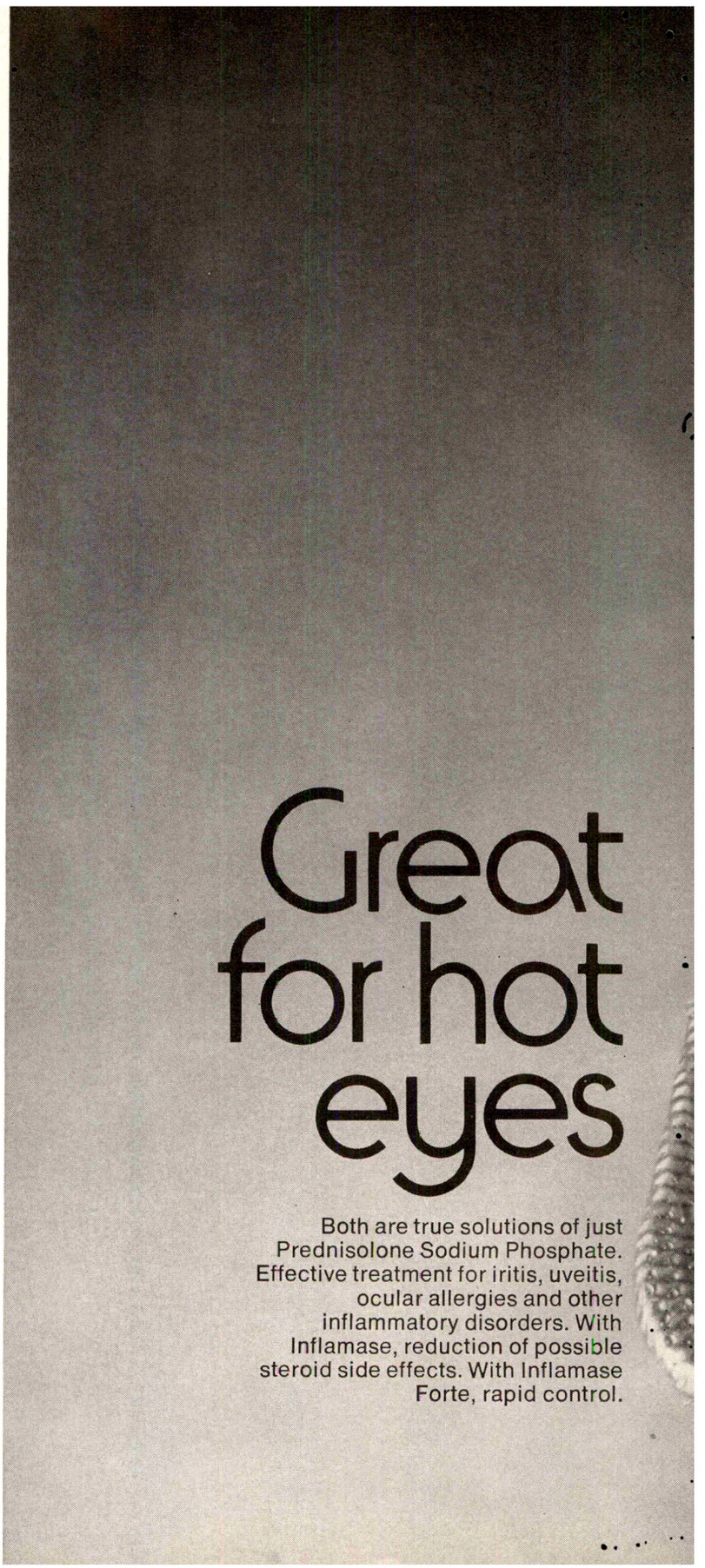
**Warning:** If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.

**How Supplied:** 5 cc plastic squeeze bottle with dropper tip. These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Store in cool place. Protect from light.

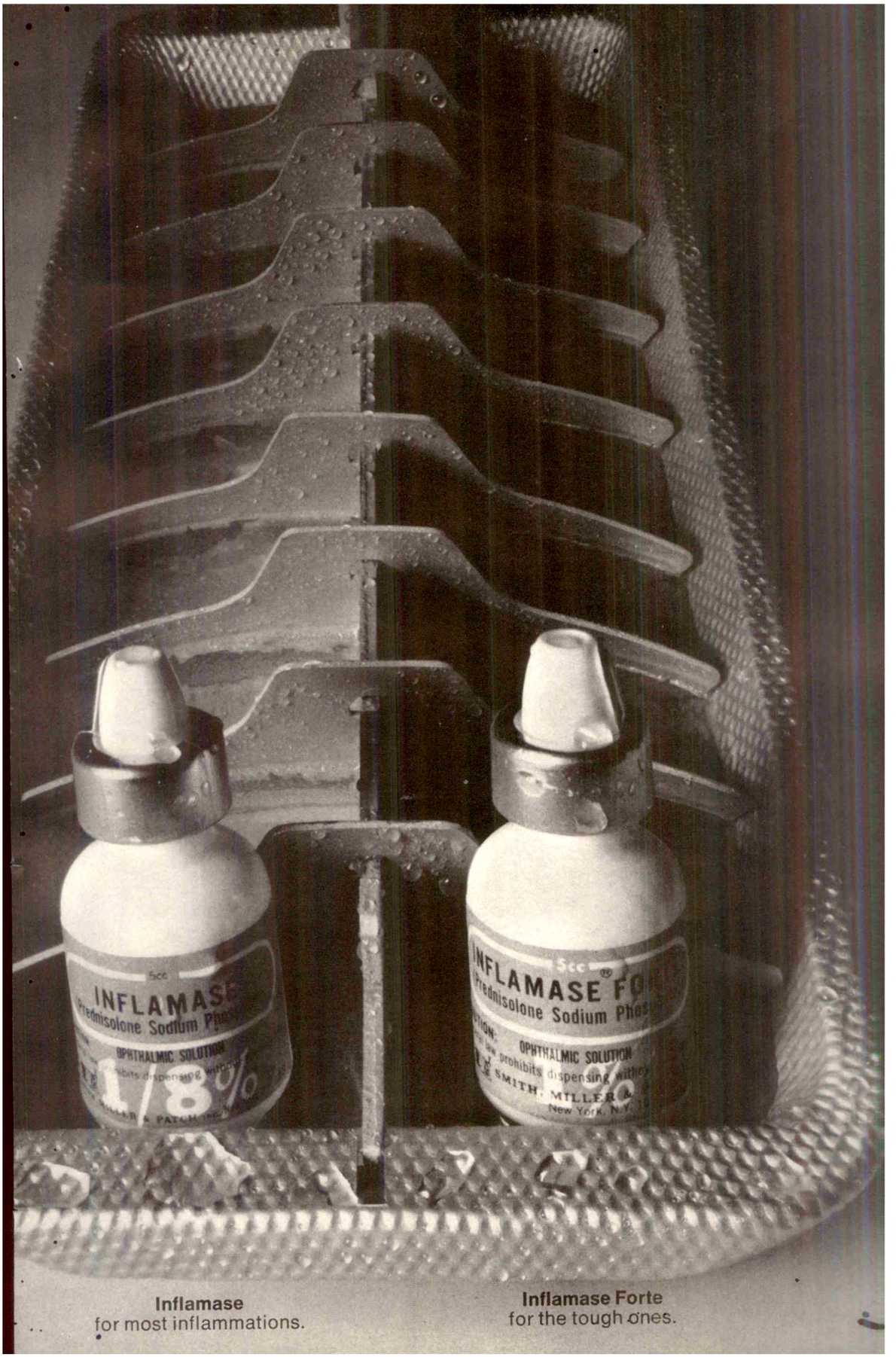
**Caution:** Federal law prohibits dispensing without prescription.

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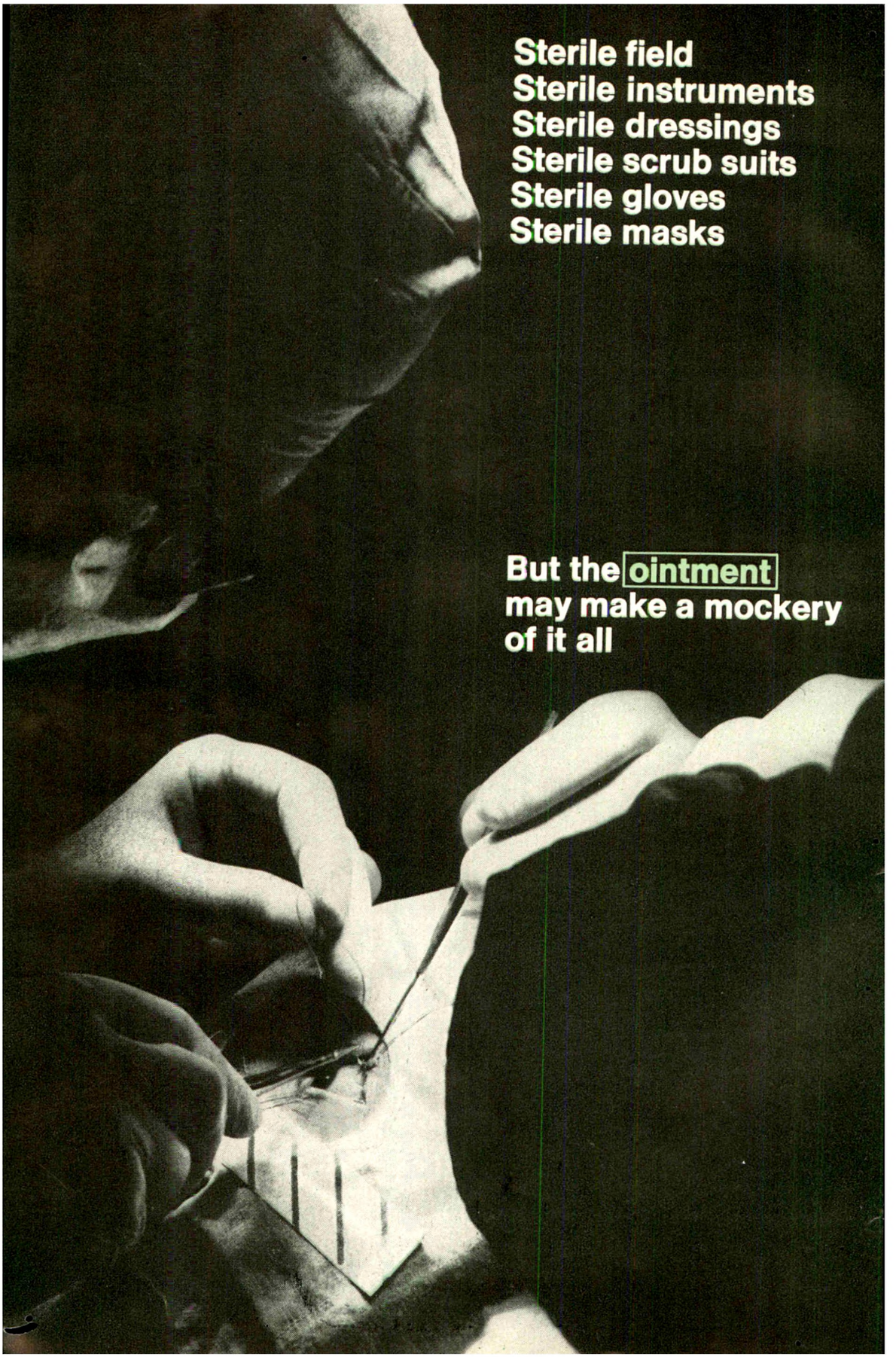
# Great for hot eyes

Both are true solutions of just Prednisolone Sodium Phosphate. Effective treatment for iritis, uveitis, ocular allergies and other inflammatory disorders. With Inflamase, reduction of possible steroid side effects. With Inflamase Forte, rapid control.




**Inflamase**
for most inflammations.

**Inflamase Forte**
for the tough ones.


Sterile field
Sterile instruments
Sterile dressings
Sterile scrub suits
Sterile gloves
Sterile masks
But the ointment
may make a mockery
of it all

**"Iatrogenic infection must be seriously considered and eliminated by all concerned insofar as it may be prudently possible. [It] . . . may result in a break in sterile surgical technique . . . Those topical products for use in the environment of the hospital should be sterile. . . ."**
**—Evans, W. J.: FDA Papers, May 1970.**

**Vander Wyk and Granston[1] reported in 1958 that 71 out of 83 (85.5%) samples of ophthalmic ointments tested were unsterile. Other investigators, notably Bowman and Holdowsky[2], and Bowman[3] have also reported on ophthalmic ointment contamination using various testing methods.**

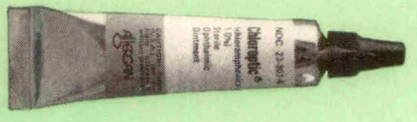


This plate was prepared from a commercially available ophthalmic ointment. The approximate number of microorganisms and the species (thereof per gram of ointment were:) Staphylococcus, 250; Achromobacter, 100; Nocardia, 50; Actinomyces, 50; Corynebacterium, 50; Bacillus, 200; Yeast, 50; Mold, 1900.



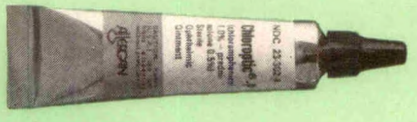
This plate shows the results obtained when one of a series of Allergan's new sterile ointments was tested using exactly the same procedure. No contamination could be detected.[4]

## Now, for the first time Allergan offers these New Sterile Ophthalmic Ointments.



### Chloroptic® (chloramphenicol) Sterile Ophthalmic Ointment

Contains: chloramphenicol . . . 1.0% (10mg/Gm) chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.



### Chloroptic™-P Sterile Ophthalmic Ointment

(chloramphenicol-prednisolone)
Contains: chloramphenicol . . . 1.0% (10mg/Gm) prednisolone alcohol 0.5% (5mg/Gm) chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.



### Atropine Sulfate 1.0% Sterile Ophthalmic Ointment

Contains: atropine sulfate . . . 1.0% with: chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.


1. R. W. Vander Wyk and A. E. Granston, *J. Am. Pharm. Assoc., Sci. Ed., 47*, 193 (1958)
2. F. W. Bowman and S. Holdowsky, *ibid., 48*, 95 (1959)
3. F. W. Bowman, *J. Pharm. Sci., 58 (2):* 277 (Feb), 1969
4. Data from research files, Allergan Pharmaceuticals, Irvine, California


ALLERGAN Pharmaceuticals Irvine, California/Montreal, Canada

# The crystal drop assures stability



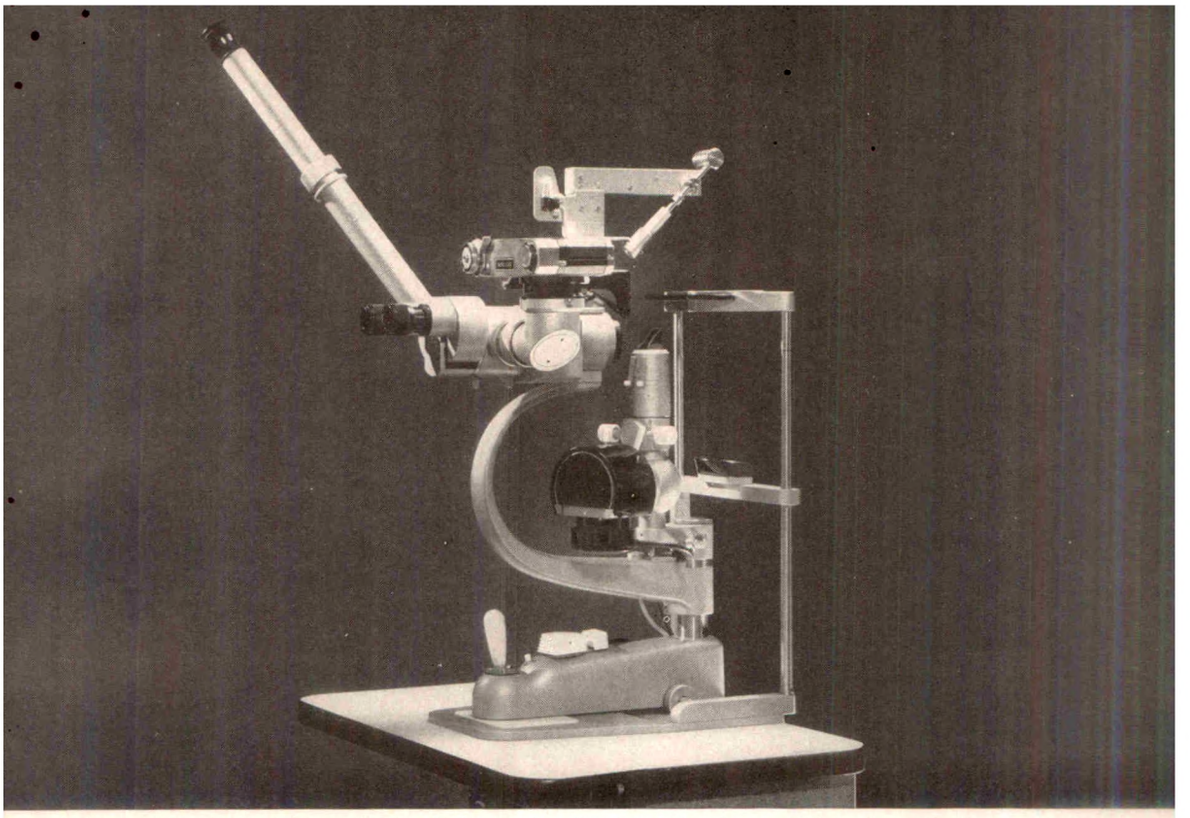

As you may be aware, the first sign of deterioration in a product containing epinephrine is a color change... reddish-brown or "yellowing." Each clear drop of PE* Ophthalmics is its own proof of stability...as also evidenced in clinical studies involving unrefrigerated shelf life, temperature changes and exposed-to-air studies simulating patient use. Proven shelf life, over 3 years (for maximum assurance, vials are date-coded on a 2 year basis). No change in clarity or potency was evidenced in any tests. The crystal clarity of every drop assures your patient full therapeutic effect, first drop to last.

PE* Ophthalmics provide simple *one-solution* treatment of open angle glaucoma... eliminating patient error, assuring the physician exact evaluation of therapy. Available in 5* strengths, in 15cc color-coded vials, nationwide and in Canada.

*Pilocarpine Hydrochloride 1%, 2%, 3%, 4%, 6% with Epinephrine Bitartrate 1% (½% Epinephrine Base).

**Contraindication:** Narrow angle glaucoma. **Precautions:** Use with caution in unverified glaucoma and hypertension. If irritation or sensitization occurs, discontinuance may be necessary.

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236 SOUTH VERDUGO RD.
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Slit Lamp PE/E with Hruby lens, fixation device, applanation tonometer, beam-splitter, observation tube and camera.

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**4 basic models**—manual and motorized, step-wise and zoom. The step-wise magnification system is from 6x to 40x (the widest range of any slit lamp from anyone), the zoom is 8x to 40x. They're called the SM/M, the PM/M, the PE/E, and, of course, the famous Photo-Slit Lamp, the ultimate in sophistication. Standard on the Photo-Slit Lamp, and available also on the other three models, is an extra-long working distance to facilitate surgical intervention.

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**A NEW PRODUCT:** Implants—Sleeves (Tubes) for preventing adhesions in Eye Muscle Surgery. Method development by Edward A. Dunlap, M.D. Reference: Dunlap, Edward A.: Plastic Implants in Muscle Surgery, Archives of Ophthalmology, 80: 249-257, August 1968.

**TUBING.** *Fully inert because it is made of the same material as the suture;
* Thinnest walls of any surgical tubing, fully transparent and can be *repeatedly* autoclaved;
* Most economical. It is in your interest to compare prices and quality.

**FOIL.** Excellent results with our suture created the demand for Foil for plastic and reconstructive surgery in such cases as orbital fractures, lid reconstruction, etc. Foil is chemically identical with the sutures, thus just as inert when buried in the tissue.

Available in thickness from 0.05mm to 2.00mm, in sheets 15 x 20cm.

Can be steam-autoclaved, cut to size, and carved to shapes and forms.

References: Merrill J. Reeh and James K. Tsujimura: Early Detection and Treatment of Blow-out Fractures of the Orbit, Am. Journal of Ophthalmology, 62: 79-82, 1966. Callahan, Alston: Reconstructive Surgery of the Eyelids and Ocular Adnexa. Aesculapius Publishing Co., Birmingham, Alabama, 1966. Cibis, Paul: Lid Reconstruction and Lifting with Fenestrated Supramid Supports. Klin. Monatsbl. Augenh., 112, 3, 1947. J. Barraquer—Z. Cuellar-Montoya: Keratoplasty: Superficial and Deep Corneal Sutures, Annal of Ophthalmology, 1:34-38, 1969. Mustarde, John C.; Jones, Lester T. and Callahan, Alston: Ophthalmic Plastic Surgery Up-To-Date. Aesculapius Publishing Co., Birmingham, Alabama, 1970.

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The new OpMi 7 is truly special in every sense of the word. It's special in that it is designed only for ophthalmological microsurgery. And special too in price—its many outstanding design features are shared only with instruments costing considerably more.

**Wide field of view:** 55 mm at 3.6x — 95% more area than other instruments in its price range.

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# in post-operative retinal or cataract surgery

## Murocoll Phenylephrine, Scopolamine and Prednisolone (Murocoll Product #2c)

**FORMULA:** Sterile ophthalmic solution containing Phenylephrine Hydrochloride 10%, Scopolamine Hydrobromide 0.3% and Prednisolone 0.2%; preservatives chlorobutanol 0.5%; sodium bisulfite; polysorbate 20 and distilled water as inactive ingredients.

**CLINICAL INDICATIONS:** Used in intraocular inflammation such as uveitis and iritis, where it is desirable to maintain dilation, rest ciliary body as well as to decrease inflammation with post-operative retinal or cataract surgery.

**CONTRAINDICATIONS:** (a) Acute herpes simplex, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva. (b) Tuberculosis. (c) Fungal diseases. (d) Acute purulent untreated infections which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid. (e) Purulent conjunctivitis and purulent blepharitis. Individuals with hypersensitivity to belladonna alkaloids.

**PRECAUTIONS:** (a) Extended use of topical steriod therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. (b) In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids.

**CAUTION:** Should be used with caution in patients with narrow chamber angles.

**DOSAGE:** One or two drops in eye three or four times daily until all signs of intraocular inflammation are absent.

Use of this combination reduces the number of instillations that would be required if separate agents were prescribed, and materially reduces the cost of therapy.

**AVAILABLE:** 7.5 cc glass bottle with plastic dropper on prescription only.

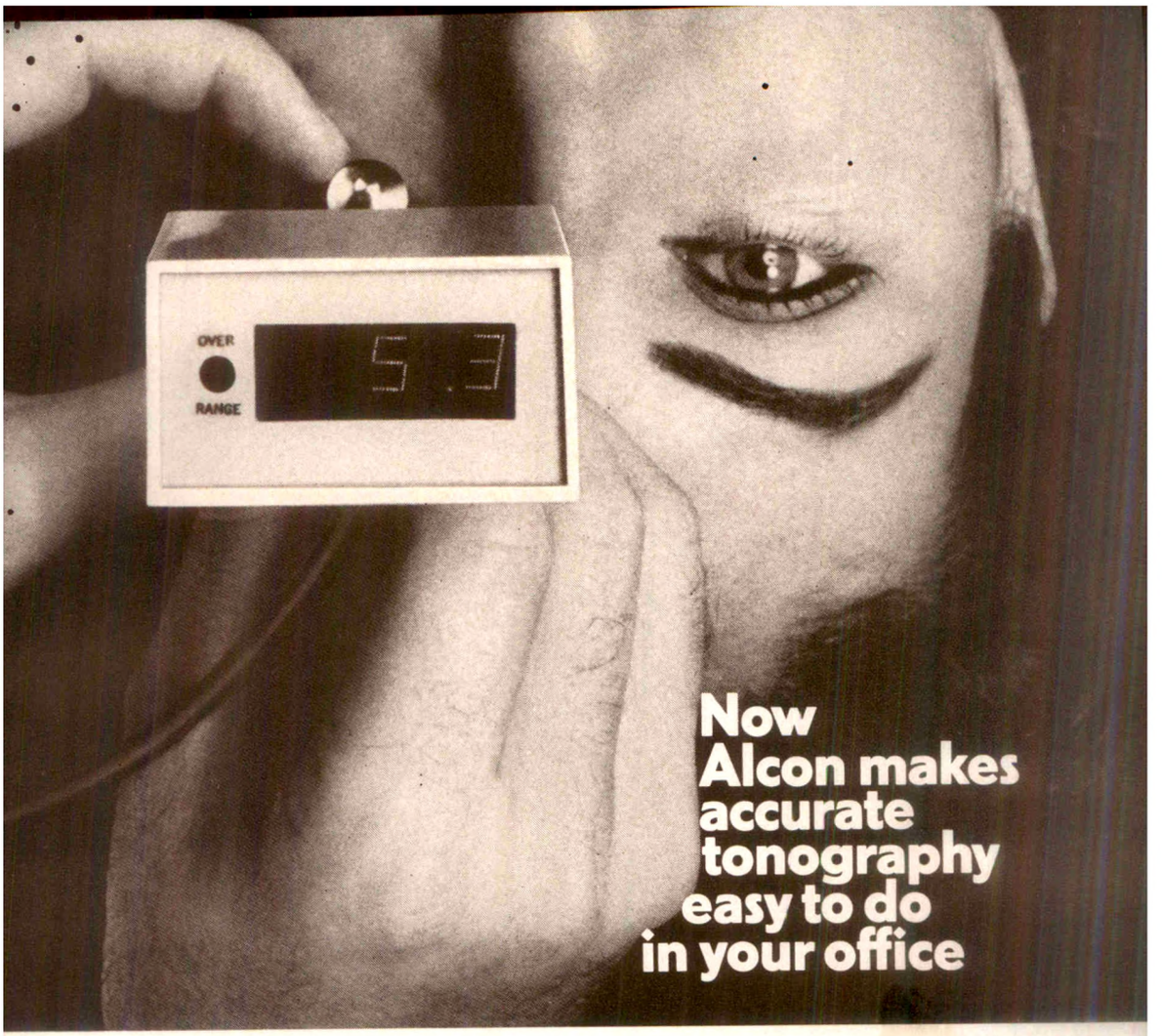
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Muro preparations are available to all community pharmacists and hospitals through their drug service wholesaler.




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**ALCON introduces the EDT-103™—the first electronic digital tonograph and automated recorder. Only the EDT-103 provides accurate, simplified tonography for routine office use. And any member of your staff can be trained to use it in less than half an hour.**

**easy to read:**
direct digital display of tonometric scale readings conveniently...at tonometer head

**easy to operate:**
self-activating recorder, automatically controlled and timed permanent patient record on "fan-fold" strip chart
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**easy to maintain:**
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all solid state circuitry
carries a one-year warranty, easily serviced
meets or exceeds all requirements of Specification 5

Write for additional information, or to have our representative arrange for a personal demonstration.



## EDT-103

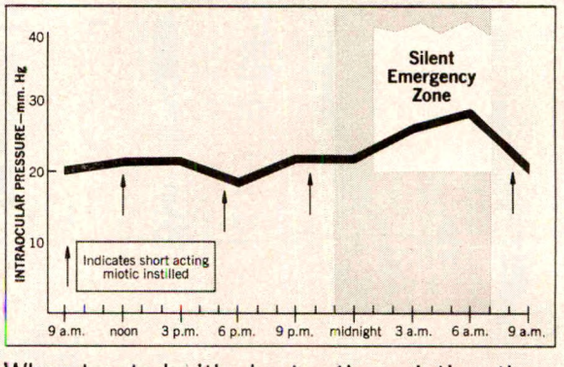
A new dimension in the detection and management of glaucoma—

Surgical Products Division, Alcon Laboratories, Inc./ P.O. Box 1959, Fort Worth, Texas 76101

# Not more potent, but longer acting...*

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

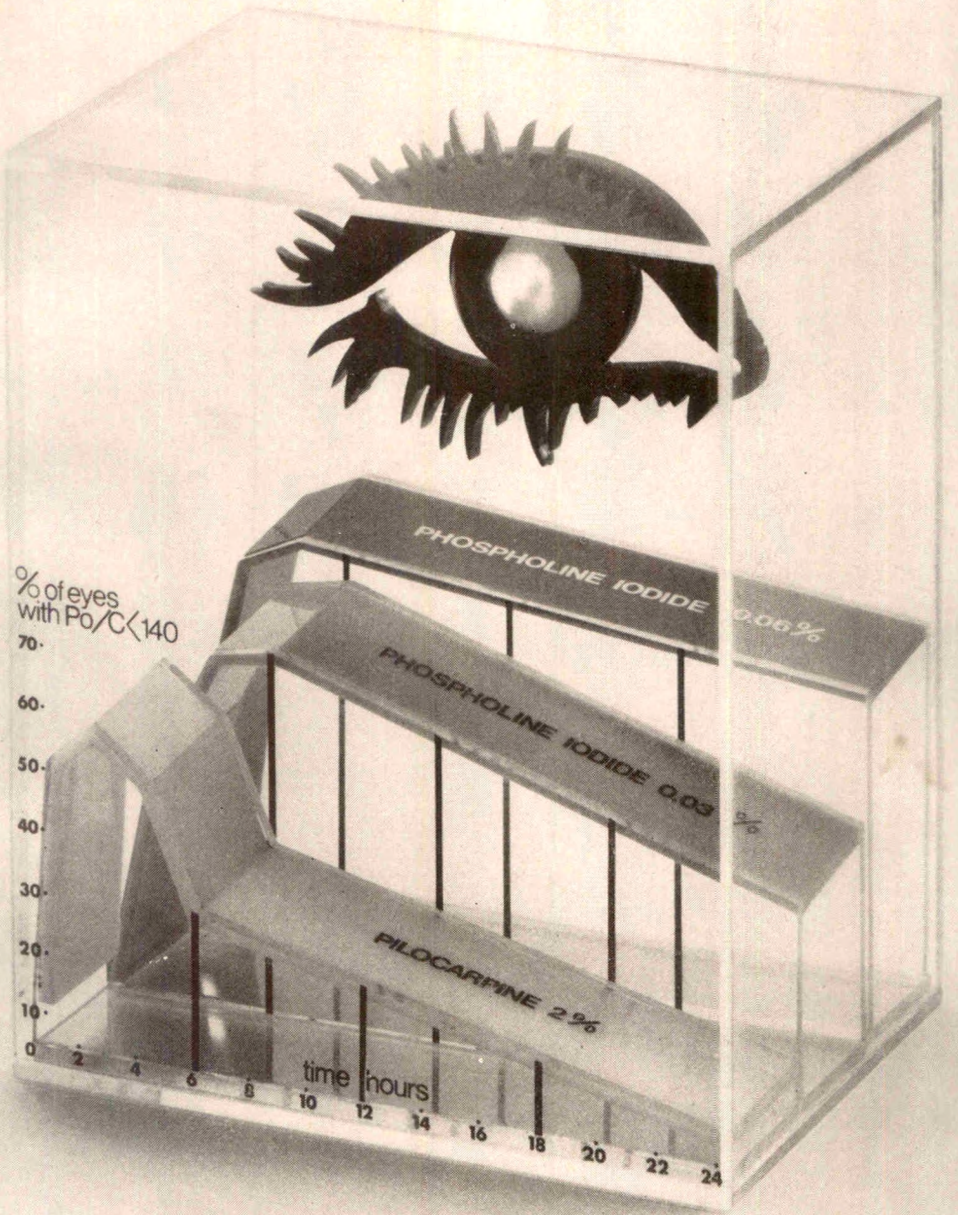



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25%—when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

for 24 hour control in chronic simple (open-angle glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, browache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

# There is still nothing like it.




The superb Donaldson* Stereo-Camera is still the standard of quality that all others try to match. None has yet.

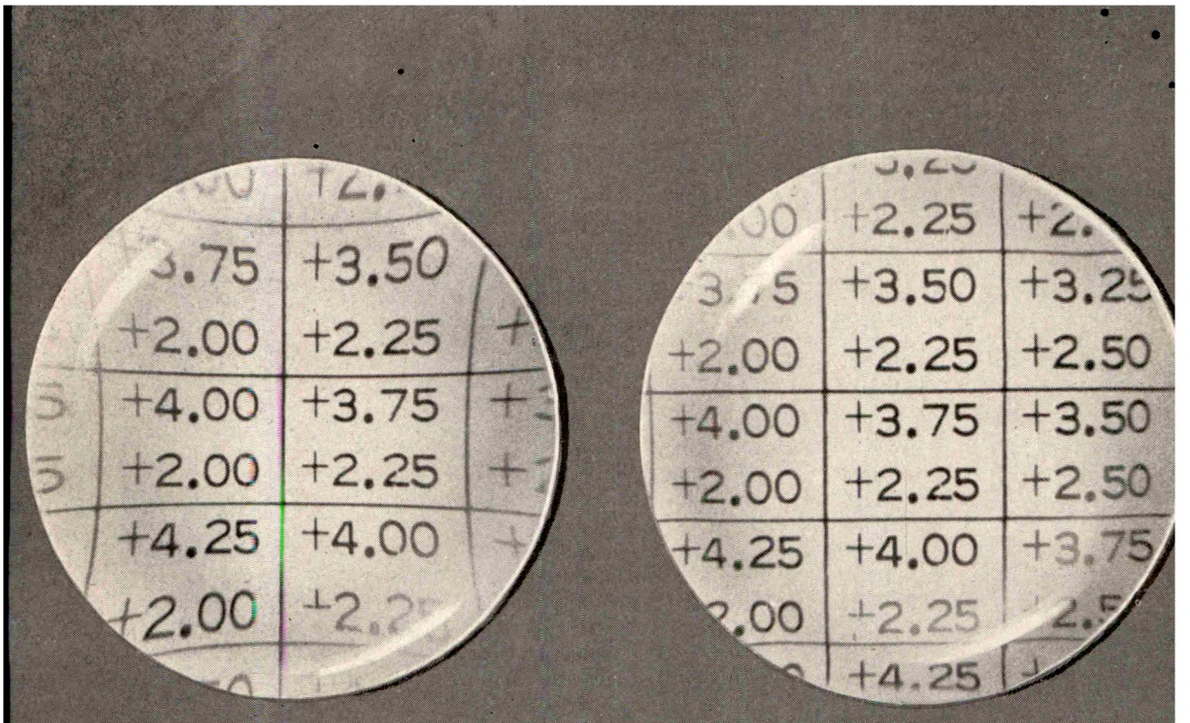
And quality means more than precision construction. The Donaldson is simple to use — you concentrate on the subject, not on complicated controls. It is versatile — you can use it for close-up photography as you would an ordinary 35mm camera. It is a complete system — with an available drum viewer, strip viewer, and single slide viewer.

As for processing, we simplify that too — both developing and mounting if you wish. And last but not least, the Donaldson Stereo-System is now available without delay. Write today for a full description and ordering information. Mentor Division, Codman & Shurtleff, Inc., Randolph, Massachusetts 02368.

*David D. Donaldson, M.D., Associate Professor of Ophthamology, Harvard Medical School, Howe Laboratory of Ophthamology and Massachusetts Eye and Ear Infirmary.

Codman Mentor DIVISION

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# BEFORE and AFTER

## YOUR PATIENT CHANGES TO ASPHERIC CRISTYL® LENSES BY TITMUS

Titmus Cataract Lenses combine advantages of aspheric curves, straight top or round segments, and featherlight Cristyl in full or lenticular field to benefit your patients *7 ways:*

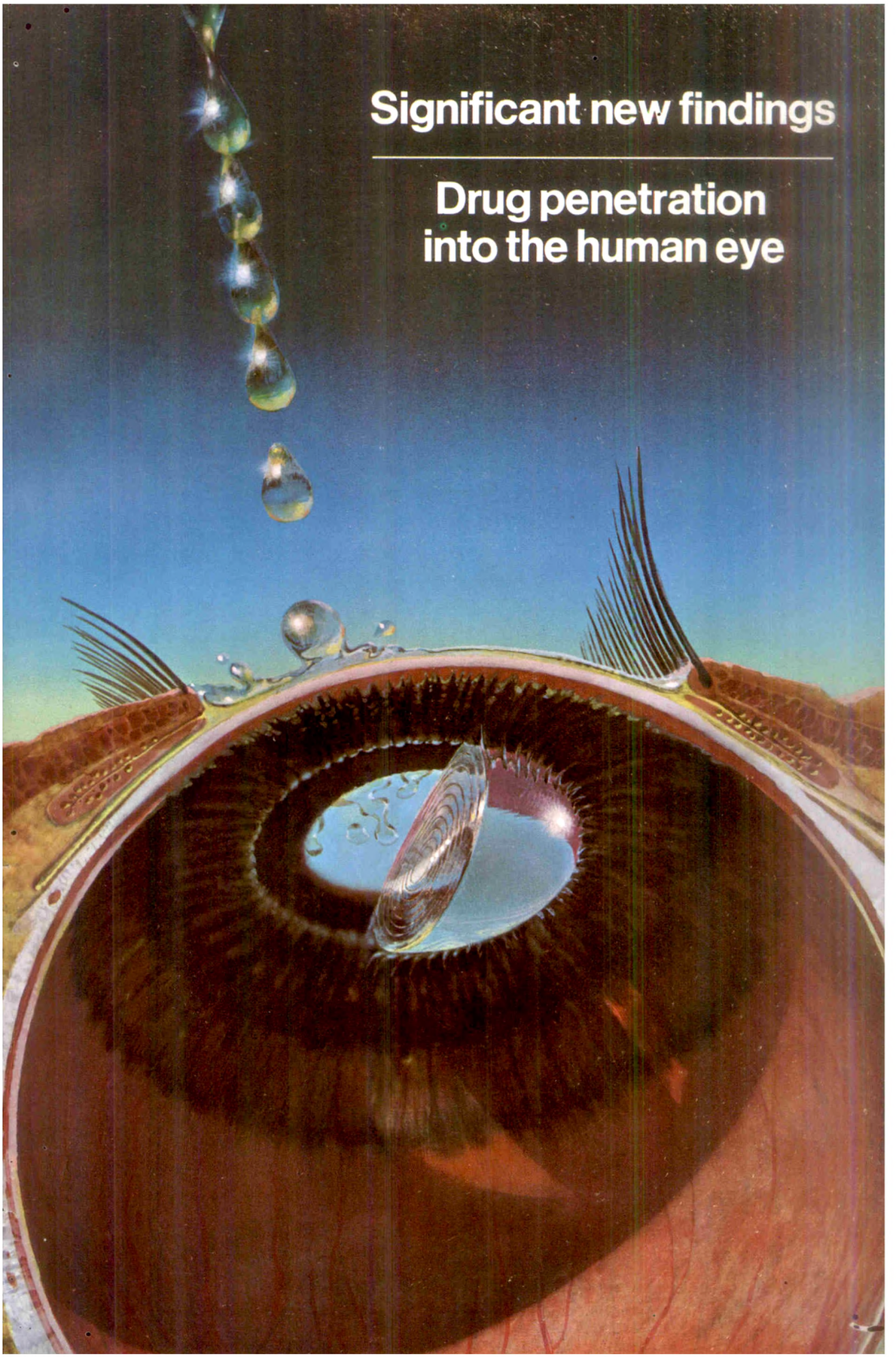
1. WIDER FIELD OF UNDISTORTED VISION—Patient moves about with increased safety and confidence.
2. STRAIGHT TOP OR ROUND SEGMENTS—Optimum design/more comfortable seeing.
3. IMPACT-RESISTANT—Safeguards eyes/protects against lens breakage.
4. REDUCED WEIGHT—Fewer adjustments/daylong comfort.
5. GREATER CLARITY—Less surface reflection/more light/improved acuity.
6. ULTRA-VIOLET PROTECTION—Even clear Cristyl absorbs harmful rays.
7. UNIFORM DENSITY TINTS—Uniform transmission from center to edge.

Cristyl®

LIGHT,
HARD,
CLEAR!

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Subsidiary of Esterline Corporation
Petersburg, Virginia 23803


Significant new findings
Drug penetration
into the human eye

# for the first time independent research relates ocular drug penetration in humans to your choice of ophthalmic vehicles

## Proof of penetration—new fluorophotometry concentration/duration study[1]

Using a slit lamp fluorophotometer, "the effects of ophthalmic vehicles on the intraocular penetration of topical fluorescein in man" were determined. "Quantitative data on ocular penetration of this drug, in man, in vivo, are presented."

### The study

Fluorescein combined with hydroxypropyl methylcellulose 0.5%, polyvinyl alcohol 1.4% and aqueous; each vehicle instilled in the eyes of 20 normal subjects; each subject served as his own control; hourly measurements of attained drug concentration were made quantitatively using a slit lamp fluorophotometer.

### The findings

CORNEA

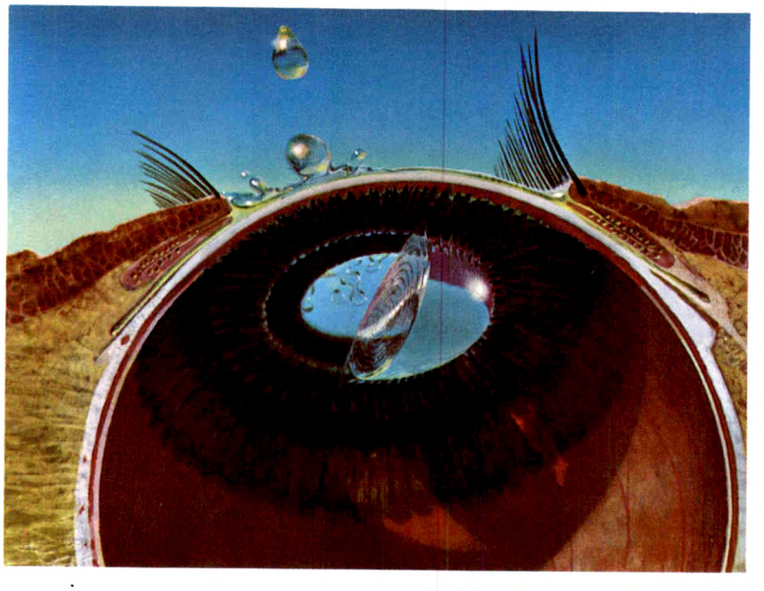
Over a three hour period, hydroxypropyl methylcellulose produced corneal drug levels 85% higher than polyvinyl alcohol and 43% higher than the aqueous vehicles.‡

AQUEOUS HUMOR

Over a three hour period, hydroxypropyl methylcellulose produced aqueous humor drug levels 93% higher than polyvinyl alcohol and 42% higher than the aqueous vehicle.‡‡

### The authentication

The authors state that their findings may, or may not, be true for drugs other than fluorescein. However, the findings reported above were achieved "consistently and reproducibly"; data were analyzed and tested for significance on a computer.



# For greater therapeutic efficacy the most potent ocular steroid...

## Maxidex®

dexamethasone 0.1%

Dexamethasone has anti-inflammatory action thirty to fifty times that of cortisone (measured in activity by weight)[3] Dexamethasone is the most potent of the corticosteroids available for ophthalmic use.

**And MAXIDEX is dexamethasone.**

**More penetration[1]**
**More concentration in ocular tissue[1]**
**Most potent ocular steroid[4]**

*Description:* Sterile preparation containing: Active: Dexamethasone 0.1%; Vehicle: Sodium Chloride, Dried Sodium Phosphate, Hydroxypropyl Methylcellulose, Polysorbate 80, Disodium Edetate, Citric Acid (to adjust pH), Purified Water; Preservative: Benzalkonium Chloride equivalent to 0.01%.

*Contraindications:* Contraindicated in acute herpes simplex, vaccina, varicella, and most other viral diseases of the cornea and conjunctiva, tuberculosis; fungal disease; acute purulent untreated infections which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid.

*Warnings:* Intensive or prolonged topical corticosteroid therapy is a possible factor in the formation of posterior subcapsular cataracts. Not recommended for long-term use in pregnant patients.

*Precautions:* Institute other therapy if inflammatory reaction does not respond within reasonable period. Discontinue use if sensitivity occurs. Extensive use of topical steroids may cause systemic side effects; ocular herpes simplex has occurred.

*Adverse Reactions:* Extended use may cause increased intraocular pressure which should be checked frequently. Perforation can occur in diseases causing thinning of the cornea.


REFERENCES:

**1.** Waltman, S.R. and Patrowicz, T.C.: Effects of Hydroxypropyl Methylcellulose and Polyvinyl Alcohol on Intraocular Penetration of Topical Fluorescein in Man, Invest. Ophthal. 9:966, 1970.

**2.** Linn, M.T. and Jones, L.T.: Rate of Lacrimal Excretion of Ophthalmic Vehicles, Amer. J. Ophthal. 65: 76, 1968.

**3.** Havener, W.H.: Ocular Pharmacology, The C. V. Mosby Company, Saint Louis, 1966.

**4.** Nelson, E.L.: "Ophthalmic Steroids," in Kaufman, H.E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970.


Alcon

dedicated to advances in ophthalmic therapy

in deep-seated ocular inflammations

# MAXIDEX®

(dexamethasone 0.1%)

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

***Caution:*** *Federal law prohibits dispensing without prescription.*

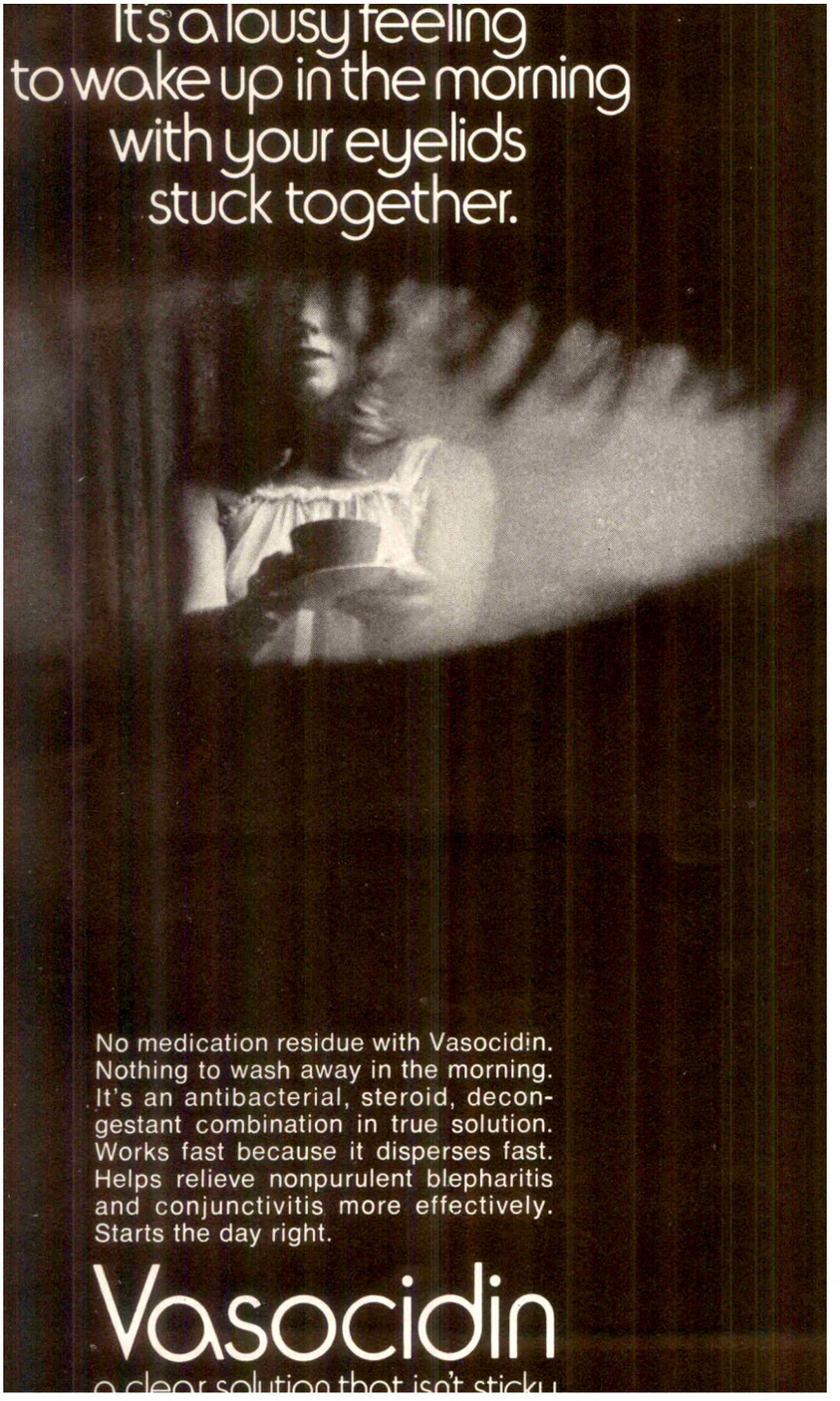
**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

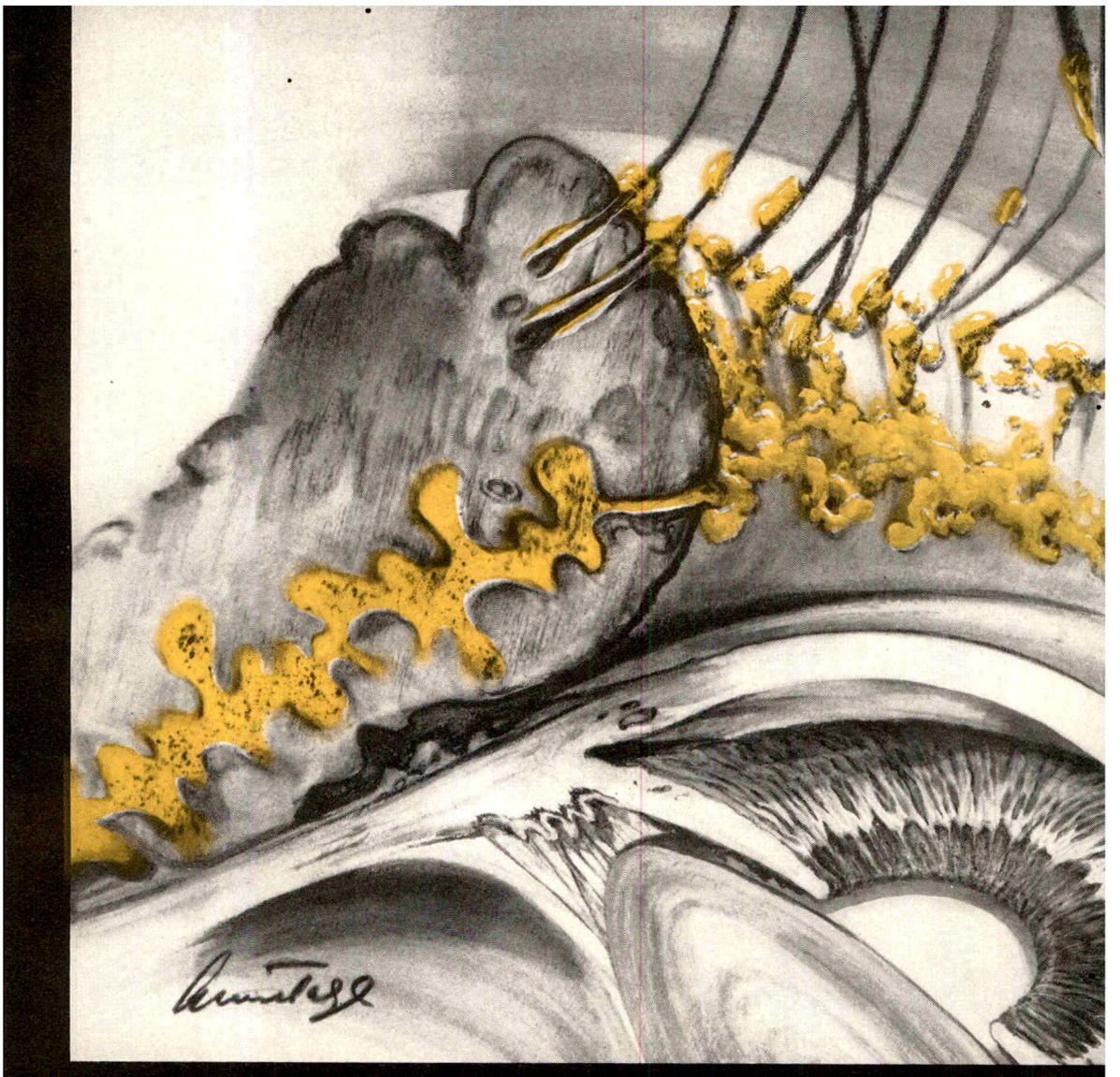
**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902


It's a lousy feeling
to wake up in the morning
with your eyelids
stuck together.
No medication residue with Vasocidin.
Nothing to wash away in the morning.
It's an antibacterial, steroid, decon-
gestant combination in true solution.
Works fast because it disperses fast.
Helps relieve nonpurulent blepharitis
and conjunctivitis more effectively.
Starts the day right.
Vasocidin
a clear solution that isn't sticky



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## Blephamide® Liquifilm®

**OPHTHALMIC SUSPENSION**

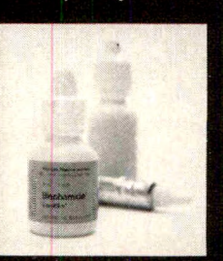
Sodium sulfacetamide, 10.0%; prednisolone acetate 0.2%; phenylephrine HCl, 0.12%; Liquifilm (polyvinyl alcohol), 1.4%; and antipyrine, 0.1%.

Specifically designed to treat nonpurulent blepharitis. Patient-accepted for routine day and night use.

With Liquifilm®—the advantage, but not the disadvantage...of ointments—prolonged contact with lesions—no greasy appearance—ointments are not required to be sterile.

Dries quickly to a clear, invisible film on lids...so cosmetically acceptable, round-the-clock treatment virtually assured.

One-prescription economy.



**Why Use Two... When One Will Do!**

With BLEPHAMIDE LIQUIFILM, you provide antibacterial/anti-inflammatory/anti-allergy/anti-seborrheic activity—in a form that has the convenience of drops...the persistence of ointments. All of the advantages of both dosage forms...none of the disadvantages.



**Description:** Sodium sulfacetamide, 10.0%; prednisolone acetate, 0.2%; phenylephrine HCl, 0.12%; Liquifilm (polyvinyl alcohol), 1.4%; phenylmercuric nitrate, 0.004%; polysorbate 80, 0.1%; antipyrine, 0.1%; with: disodium edetate; sodium phosphate; dibasic anhydrous sodium phosphate; monobasic sodium thiosulfate; purified water; hydrochloric acid to adjust pH to 6.8.

**Indications:** Nonpurulent blepharitis and blepharoconjunctivitis (seborrheal, staphylococcal, and mixed); nonpurulent conjunctivitis (allergic and bacterial).

**Contraindications:** Acute herpes simplex (dendritic keratitis), purulent untreated infections, vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, ocular tuberculosis and fungal diseases of the eye.

**Warnings:**

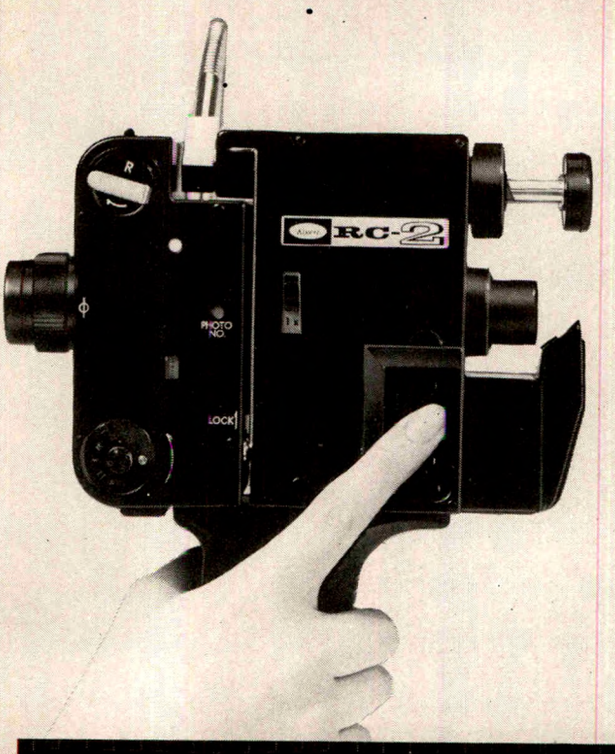
1. In diseases due to microorganisms, infection may be masked, enhanced or activated by the steroid.
2. Extended use may cause increased intraocular pressure in susceptible individuals. It is advisable that the intraocular pressure be checked
3. In those diseases causing thinning of the cornea perforation has been known to have occurred with the use of topical steroids.
4. Use with caution in patients with known or suspected sensitivity to sulfonamides — if sensitivity or other untoward reactions occur, discontinue medication.
5. Should be used with caution in the presence of narrow angle glaucoma.
6. Reports in the literature indicate that posterior subcapsular lenticular opacities have been reported to occur after heavy or protracted use of topical ophthalmic steroids.

**Dosage and Administration:** 1 drop 2 to 4 times daily, depending on the severity of the condition.

**Supplied:** 5 cc. and 10 cc. plastic dropper bottles — on prescription only.

ALLERGAN Pharmaceuticals

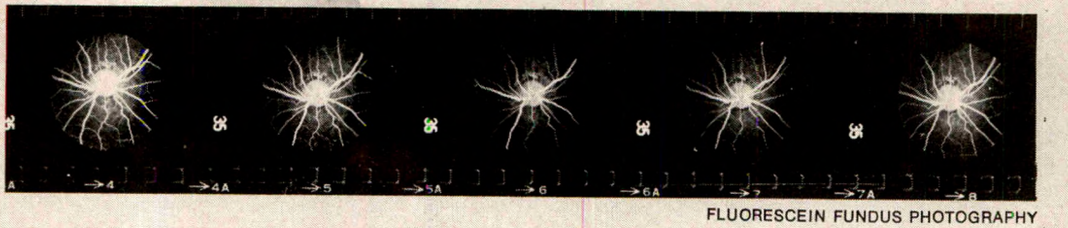
Irvine, California/Montreal, Canada




# Kowa RC-2

## fundus camera

*The simple approach to fundus and fluorescein photography.*




FLUORESCEIN FUNDUS PHOTOGRAPHY

To be fully meaningful to the medical profession, all instrumentation must function as an extension of the user's eyes, hands, and mind. The Kowa RC-2 fundus camera fully embodies this principle.

• *Fundus and External Photography* The basic RC-2 incorporates every conceivable advance in optics, mechanics, and electronics. Standard are built-in flash, 2X magnifying lens, automatic frame numbering for patient coding, and more. It will produce impeccable 35mm results even for inexperienced users.

• *Fluorescein Photography* By simply adding an auto-wind back, filters, and a quick-cycling power unit, the RC-2 becomes a flawless fluorescein photographic instrument.

• *Polaroid® Photography* An attachment gives you 60-second fundus photographs.

To see why the *total systems approach* has made Kowa's RC-2 the standard by which all others are measured, contact the representative in your area.

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**STOXIL®**
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the only brand of IDU
available in two forms:
Solution—Ointment

Both now available in Canada




# The choice is yours

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

**Description: 'Stoxil' Ophthalmic Solution** contains idoxuridine (5-iodo-2'-deoxyuridine) **0.1% (1 mg./cc.)** in distilled water. Preserved with thimerosal, 1:50,000. **'Stoxil' Ophthalmic Ointment** contains idoxuridine **0.5% (5 mg./Gm.)** in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

**Contraindications:** Contraindicated in patients with known or suspected hypersensitivity to any of its components.

**Precautions:** Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of the therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

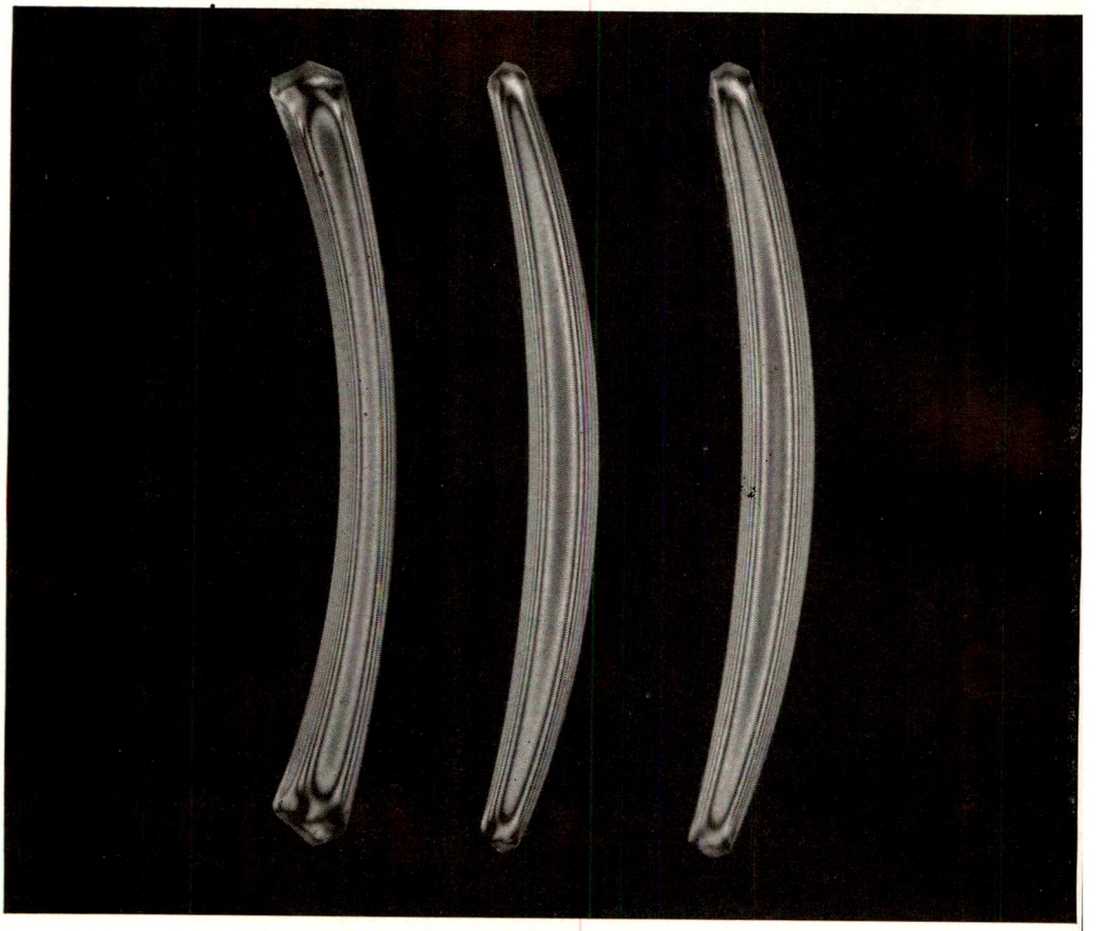
**Adverse Reactions:** Occasionally, irritation, pain, pruritus, inflammation, edema of eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

**How Supplied:** 0.1% Ophthalmic Solution (1 mg./cc.), in 15 cc. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./Gm.) in 4 Gm. tubes.

**Stability:** The Ophthalmic Solution should be stored in refrigerator until dispensed. 'Stoxil' Ophthalmic Ointment does not require refrigeration.

SK&F Smith Kline & French Laboratories

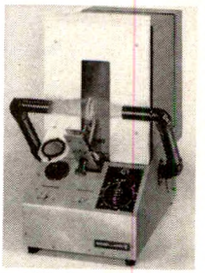
# locked-in confidence



## A Closed Envelope of Compression Means Full Impact Resistance from Center to Bevel Crown

Legislation requiring impact-resistant lenses in all prescriptions is on the books in several states. A federal regulation requiring them is being considered. And with these acts comes the unsettling question of responsibility and liability for the protective lenses you dispense.

This unique and unretouched photograph shows in cross section three lenses heat-treated in a B&L Compact Heat-Treating Unit. Polarized light reveals the evenly balanced, compression-expansion stress structure that imparts so much extra strength. The continuous dark line marks the boundary between tension and compression layers. You can see that the compression layer is closed and uniformly thick; there are no openings for tension "leaks" or soft spots to give way under a tension shift.



B&L Compact Heat-Treating Unit gives you lenses with no tension "leaks."

This kind of structural uniformity is possible only with the even, low turbulence quenching of the exclusive B&L large-orifice, high air-volume process. A Compact Heat-Treating Unit produces lenses which have impact resistance far in excess of all legal or proposed standards.

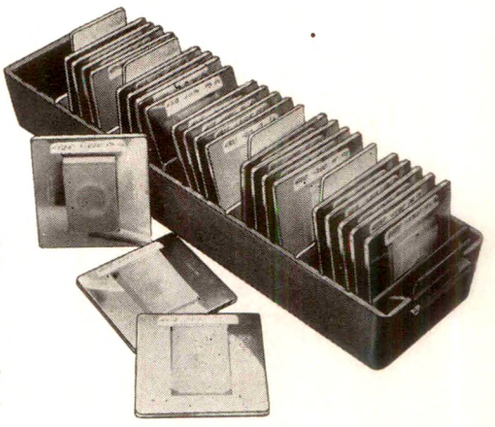
Experience the confidence of dispensing the locked-in strength of lenses treated in a B&L Compact Unit. Ask your B&L Branch or B&L Distributor about this.

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**Contact Lens Diagnostic Sets**

*(*As suggested in the text, Corneal Contact Lenses, Ed. by Girard, L. J., Sampson, W. G., Soper, J. W.— C. V. Mosby Co.)*



A set of optically perfect (Modern Arc inspected) diagnostic corneal lenses — each lens is finished in exacting reproducible detail.

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*For reprints: Sampson, W. G., Soper, J. W. — Use of Diagnostic Corneal Lenses in Aphakia and other high Ametropias; Southern Medical Journal, Apr. 1966.*

*Write*

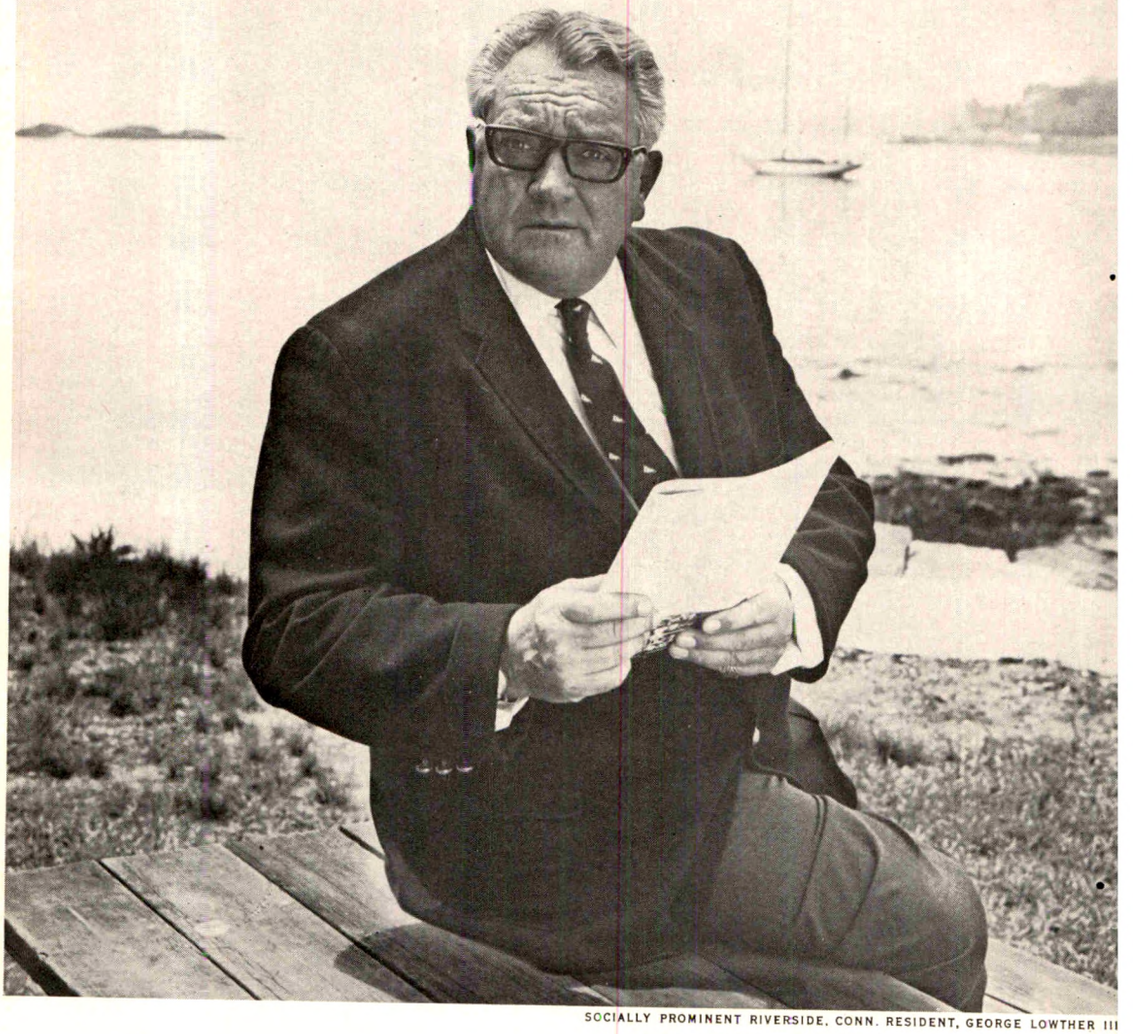
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**665**

*The* chair with the features you find only in chairs costing up to $2,495. Write for complete catalog. F. & F. Koenigkramer, 96 Caldwell Dr., Cincinnati, Ohio 45216. Dept. AJ-7

**Reliance**

# Who says Younger Lenses are only for women?



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"When my eyes were examined recently, I was told that I needed bifocals. Maybe I did, but I didn't like the idea . . . why show that I'm getting older?

"I mentioned this and was told about Younger Seamless Lenses. It made good sense. As long as I can see well for reading and distance, it doesn't bother *me* that there are two different powers in my lenses, *as long as they don't show!*

"Call me vain if you will, but good vision and no change in appearance were all I asked and that's exactly what I've got with my Younger Lenses.

"I'm told women ask for them and I can understand why. After all, my wife now wears Youngers and it pleases me to know that *her* age doesn't show, either. But I can't understand why more men aren't wearing them, unless they aren't told about their advantages."

**Younger Lenses are available through most independent labs and all American Optical branches . . . in glass or hard resin.**

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MANUFACTURING CO.
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BVI

# HARD TIMES

Although U.S. academic institutions have been able to increase their spending for scientific research and education by an average of 8% per year in 1969 and 1970, the Federal Government accounted for only 2.4% of the increase both years. In 1970 about 40% of the total support for academic science was supplied by the Government. The difference between the 2.4% increase in Federal support and the average 8% increase in expenditures was made up by funds from a combination of sources: state governments, increases in student tuition and fees, foundation grants and private gifts. In terms of constant dollars the average increase of 8% per year in spending reduces to 5%. And when increases in college enrollments (13% in the two-year period) and operating costs are taken into account, the net effective support for academic science dropped at least 5% and more likely 10% between 1968 and 1970. These conclusions were reached by the National Science Foundation after it had sent questionnaires to 104 institutions granting doctoral degrees in science and had received replies from 662 science departments.

The hardest hit were large universities and private institutions, which were able to increase their science budgets by only 4% in the fiscal year 1970, compared with an average increase of 8.5% for all institutions and 10.9% for state universities. Overall the departments reporting the smallest increases in 1970 were physics and electrical engineering (1%), biological sciences and microbiology (4%), and biochemistry and sociology (6%). The departments with the largest increases were psychology (12%) and economics (16%). Nearly a third of the responding institutions said their life-science departments were most seriously hurt by the loss of Federal funds. Twenty-one percent said physics departments were most affected; 19% cited chemistry departments.

The number of teachers and postdoctoral fellows increased by only about 3.7% in 1970 as against 6.5% in 1969. The number of graduate students fell by somewhat less than 1% both years, except that the number supported by Federal funds dropped by 2.7% in 1969 and 5.1% in 1970. In the field of mathematics the number of graduate students supported by the Federal Government fell by 9.8% both years.

*Scientific American*
May, 1971

# *TRY OUR NEW MATH !*

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2 MODERN STYLES, for Men and Women

10 SIZES, from 42 to 48, for precise comfortable fitting

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All adds up to the best temporary cataract glasses !

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FOR CATARACTS

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ACTUAL SIZE

## NO MORE ACCIDENTAL ADHESIONS!

ONCE YOU GRASP THE LENS, AT NO TIME DOES THE IRIS OR ANY OTHER TISSUE ADHERE TO THE PROBE, EVEN WHEN THERE IS DIRECT CONTACT!. THIS EXCEPTIONAL ADVANTAGE IS DUE TO ITS SPECIALLY DESIGNED TIP.

OTHER IMPORTANT ADVANTAGES:

- Thin tip (2.75 mm.) with special shape for better visibility.
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- Heat - resistant, so it can be autoclaved repeatedly.
- Durable, it can be used a great number of times.
- Rechargeable, uses gas *"FREON" 12; commercially available.
- Low price.

Ref. : Covelli B. Am. J. Ophth., 69:3, 1970
Presented at the VII Pan-Am. Congr. Ophth., Bogota, 1971

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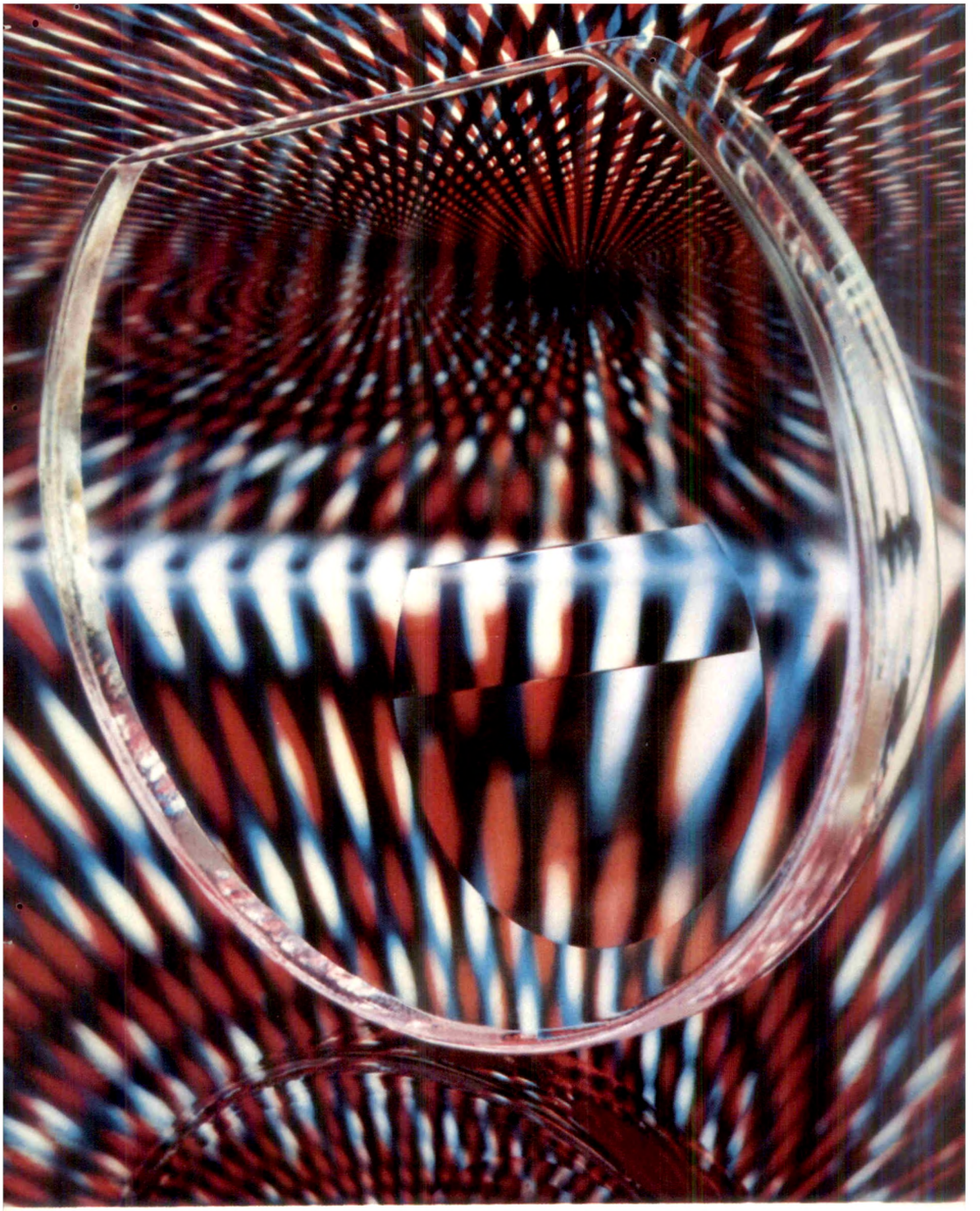
Rapid de-frost is important. The surgeon needs that element of control in retinal detachment procedures and in cataract operations. Its importance increases with every additional "plus feature" that the Amoils system employs with it. The Amoils System is a complete system with due emphasis on safety, efficiency, economy, simplicity and performance. All the pencils are light and manoeuvrable but lose no strength or robustness because of it. They are all flash autoclavable. Accidental adhesions are eliminated because the pencils are applied warm to tissue before freezing starts. The Amoils Ophthalmic Cryo Unit is important because of its superiority, and it's superior because of the unique combination of individual features, like rapid de-frost.

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# Your Heart Association can help you help your patients

Your patients and their families might have questions about the heart and blood vessel diseases. Your Heart Association has prepared a variety of pamphlets to assist you in answering their questions in simple non-technical language.

Produced under the guidance of leading cardiovascular specialists, these pamphlets deal with such subjects as heart attack, stroke, hypertension, rheumatic fever, congestive failure, inborn heart defects, varicose veins and other disorders. There are also pamphlets advising on risk factors related to heart attack.

Booklets on therapeutic sodium-restricted or cholesterol-lowering diets are also available on a physician's prescription only.

Ask your local Heart Association for a catalogue listing all these free materials and order a supply.

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*Contributed by the Publisher*

# A singular new antibiotic for the eye that works the way you think it should

## GARAMYCIN® brand of GENTAMICIN SULFATE OPHTHALMIC SOLUTION/OINTMENT



Each cc. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

## You think it should have a wide antibacterial spectrum

GARAMYCIN's wide range of antibacterial action is equal to the spectrum commonly prescribed in the combinations of neomycin, polymyxin and bacitracin or gramicidin in the treatment of external eye infections due to susceptible organisms. It has activity against a wide variety of both gram-positive and gram-negative organisms, including the "difficult" ones—*Pseudomonas aeruginosa* strains and Proteus.

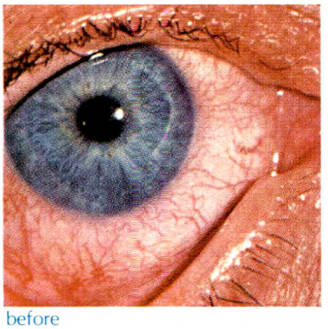
## You think it should be a single entity antibiotic

GARAMYCIN is a single entity antibiotic with a low incidence of sensitization or resistance*—can be used repeatedly with continued effectiveness, less concern about allergic potential (*Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.)

## You think it should be clinically effective

GARAMYCIN OPHTHALMIC has been described as appearing to be "...an antibiotic of choice for the initial treatment of external ocular infections."[1] It has "proved highly effective...for a wide variety of common bacterial eye infections..."[2] (due to susceptible organisms).
(1. Gordon, D.M.: Amer. J. Ophthal. 69:300 [Feb.] 1970. 2. Magnuson, R. H., and Suie, T.: JAMA 199:427 [Feb. 6] 1967.)

In acute catarrhal conjunctivitis and episcleritis† due to *Staphylococcus aureus* coagulase negative

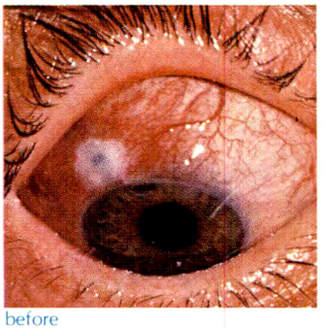


before



after 7 days GARAMYCIN OPHTHALMIC SOLUTION

In infected bleb (post-glaucoma surgery)† due to *Staphylococcus aureus* coagulase negative and *Streptococcus viridans*



before

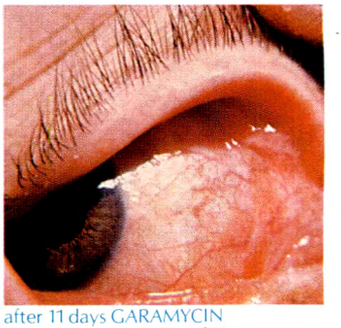


after 9 days GARAMYCIN OPHTHALMIC SOLUTION

In acute conjunctivitis and dacryocystitis†† due to pneumococcus



after 7 days GARAMYCIN OPHTHALMIC SOLUTION



after 11 days GARAMYCIN OPHTHALMIC SOLUTION

# New GARAMYCIN® ophthalmic

brand of GENTAMICIN SULFATE SOLUTION/OINTMENT

†Photographs courtesy of D. Gordon, M.D., N.Y. ††Photographs courtesy of S. Fox, M.D., Baltimore, Md.

# You think it should have flexibility in dosage forms

GARAMYCIN OPHTHALMIC SOLUTION, sterile, isotonic, and buffered to pH of tears, does not blur vision, is well suited to daytime use—supplied in an unbreakable, easy-to-handle dispenser.

GARAMYCIN OPHTHALMIC OINTMENT provides gentle emollient action and keeps medication in contact with tissues for longer periods. It is particularly advantageous for nighttime use or in non-ambulatory patients—supplied in easy-to-use ophthalmic tube.

## Clinical Considerations

**Description:** GARAMYCIN is a bactericidal antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN Ophthalmic Solution is a sterile aqueous solution buffered to approximately pH 6.7 for use in the eye. Each cc. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN Ophthalmic Ointment contains, in each gram of ointment, gentamicin sulfate (equivalent to 3.0 mg. gentamicin), and methylparaben and propylparaben as preservatives in a bland base of clear petrolatum.

Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

**Indications:** GARAMYCIN Ophthalmic Solution and Ointment are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

**Contraindications:** GARAMYCIN Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of the components of these preparations.

**Precautions:** Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

**Dosage and Administration:** GARAMYCIN Ophthalmic Solution: One or two drops every four hours. In severe infections, dosage may be increased to as much as two drops once hourly.

GARAMYCIN Ophthalmic Ointment: Apply a small amount to the affected eye two to three times daily.

**How Supplied:** GARAMYCIN Ophthalmic Solution, 5 cc. plastic dropper bottle, sterile, box of 1. GARAMYCIN Ophthalmic Ointment, 1/8 ounce tube, box of 1.

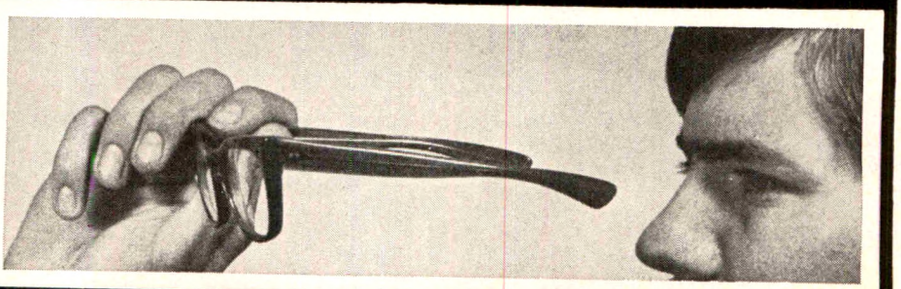
Note: Store away from heat.




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# SHIELD OR HAZARD...?



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# Control cost as well as pressure

Patients will welcome the economy of Pilocar Twin Pack. An especially important consideration for the glaucoma patient who must use pilocarpine month after month. You'll welcome the therapeutic flexibility afforded by the wide range of available potencies. Good reasons to prescribe Pilocar Twin Pack when initiating pilocarpine therapy or changing potency.

**COMPOSITION:** Pilocar Twin Pack Ophthalmic Solutions are buffered, isotonic, stabilized solutions of Pilocarpine Hydrochloride and Hydroxypropyl Methylcellulose. The solutions are available in concentrations of ½%, 1%, 2%, 3%, 4% and 6% Pilocarpine Hydrochloride. All the concentrations, in addition to the respective amount of the Pilocarpine, contain:

Hydroxypropyl Methylcellulose .....0.33%
Benzalkonium Chloride .....0.01%
Disodium Ethylenediamine Tetraacetate ..0.01%

In an aqueous isotonic, buffered, stabilized solution containing potassium chloride, boric acid and sodium carbonate.

**INDICATIONS:** As a miotic in the treatment of Glaucoma, more specifically, the chronic simple Glaucoma of the open angle type. While the closed angle Glaucoma differs completely from the open angle Glaucoma, Pilocar Ophthalmic may be used to relieve the tension in patients seen early, during hospital diagnostic tests and prior to surgery.

The most prevalent clinical application for Pilocar is in the treatment of Glaucoma Simplex (open angle or chronic Glaucoma). Pilocar acts as a miotic to contract the pupil and reduce the intraocular pressure, thereby attaining the desired relief.

In acute Glaucoma, the objective aims at opening the anterior chamber to lower intraocular pressure by medical means, i.e., Pilocar, for at least 12 hours prior to emergency surgery.

**DOSAGE AND ADMINISTRATION:** The initial dose is one or two drops. This is repeated up to six times daily depending on individual response. During acute phases, the miotic must also be instilled into the unaffected eye, as it may be subject to an attack of angle closure Glaucoma.

The frequency of instillation and the concentration of the Pilocar depends on the severity of the Glaucoma and response of the patient. The Ophthalmologist must ascertain just how much miotic is necessary for each individual patient, in much the same way that the Physician determines how much insulin is necessary to stabilize a patient's diabetes. The most widely used concentrations are the 1% and 2%.

**CRITERIA OF EFFECTIVENESS:** Treatment is continued as long as the intraocular pressure is controlled and there is no visual deterioration as indicated by changes in the visual fields. If the pressure tends to be on the high side or normal and there is no change in the visual fields, patients may be maintained on the miotic therapy indefinitely. No patient should use more of the miotic drug than is necessary to satisfactorily control the pressure.

**CAUTION:** Federal law prohibits dispensing without prescription.

**FOR TOPICAL OPHTHALMIC USE ONLY:** If irritation persists or increases, patients should be advised to discontinue use and consult a physician.

Pilocar Ophthalmic Solutions are sterile when packaged. To prevent contaminating dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly covered when not in use.

**HOW SUPPLIED:** Two 15 cc. polyethylene dropper-tip bottles—½%, 1%, 2%, 3%, 4% and 6% concentrations.

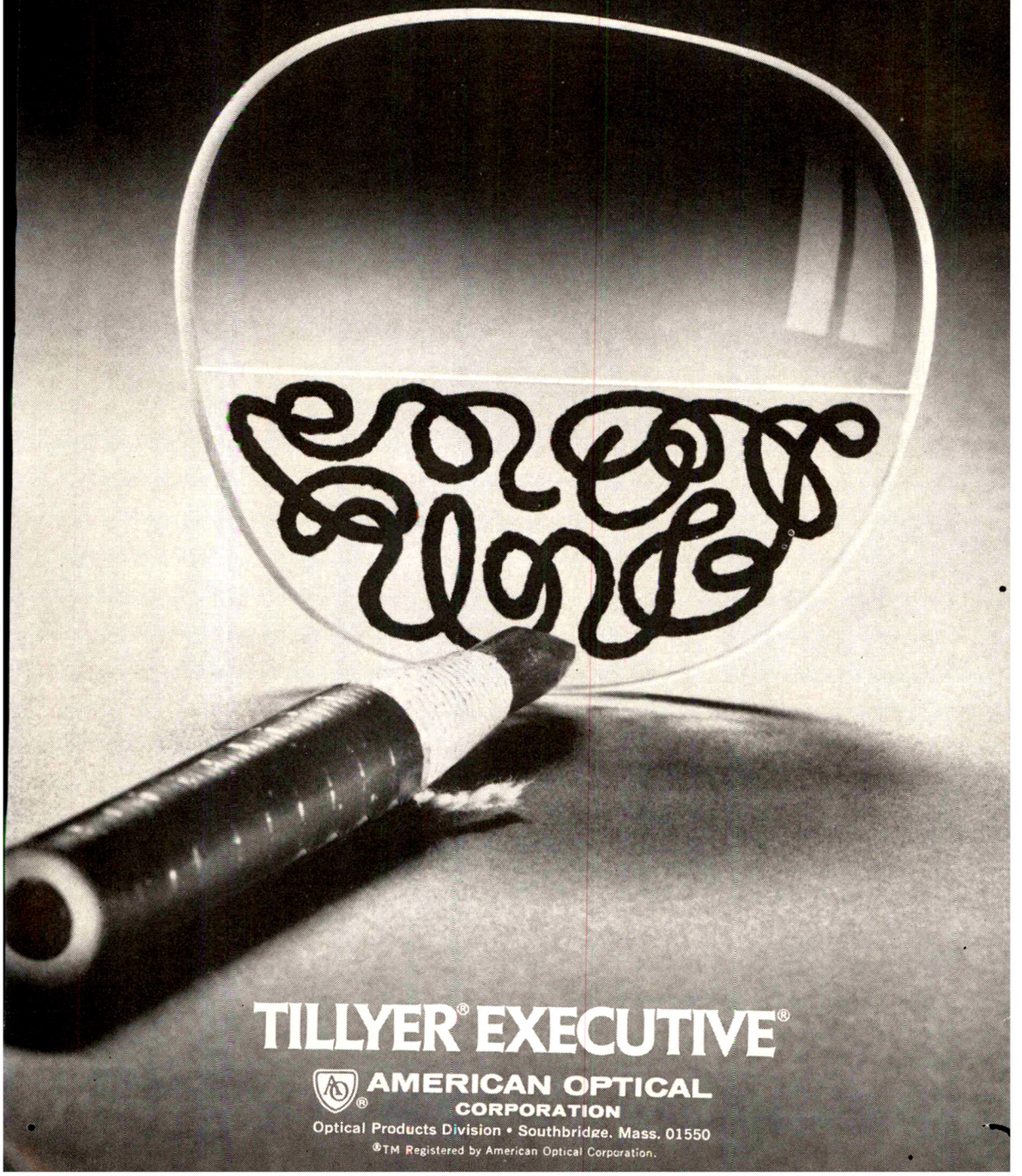
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**Pilocarpine HCl**



# The bifocal that lets your patients' eyes wander without getting lost.



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AMERICAN OPTICAL CORPORATION

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# one drop of Albalon provides over 190 minutes of the most potent decongestant activity.

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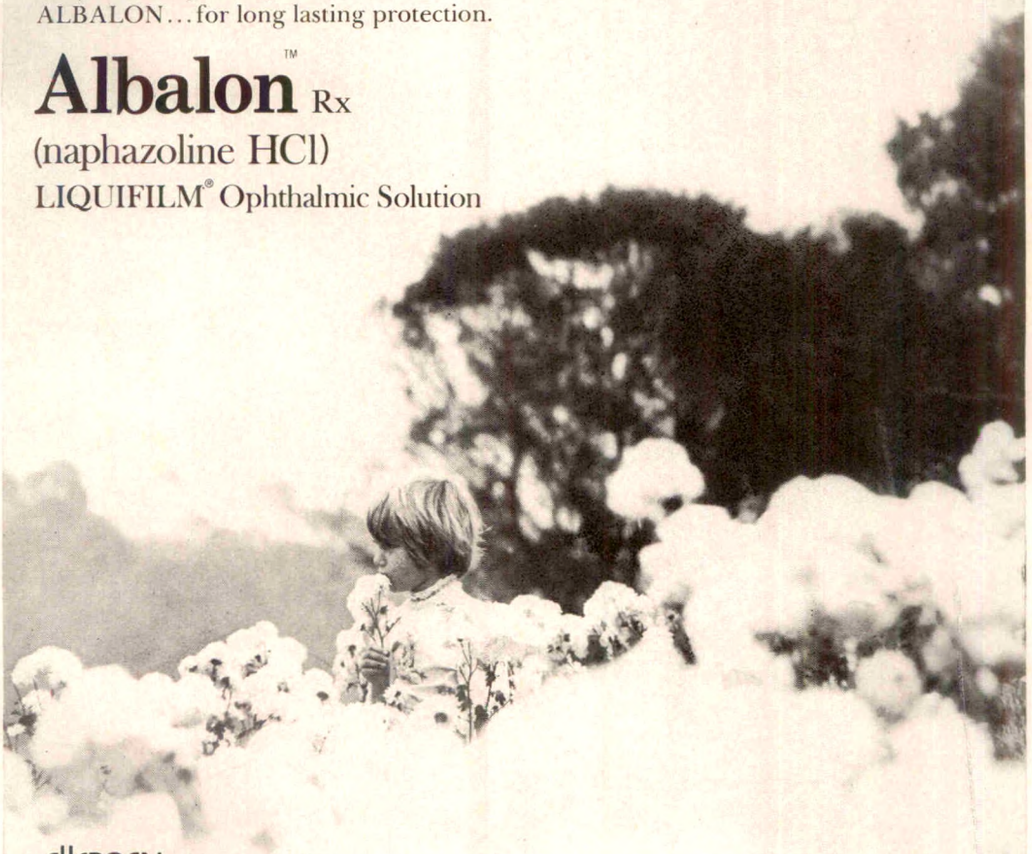
Additionally, Albalon comes in the Liquifilm vehicle to soothe, lubricate and comfort itchy, smarting, red eyes.

ALBALON... for long lasting protection.

**Albalon™ Rx**

(naphazoline HCl)

LIQUIFILM® Ophthalmic Solution



ALLERGAN Pharmaceuticals

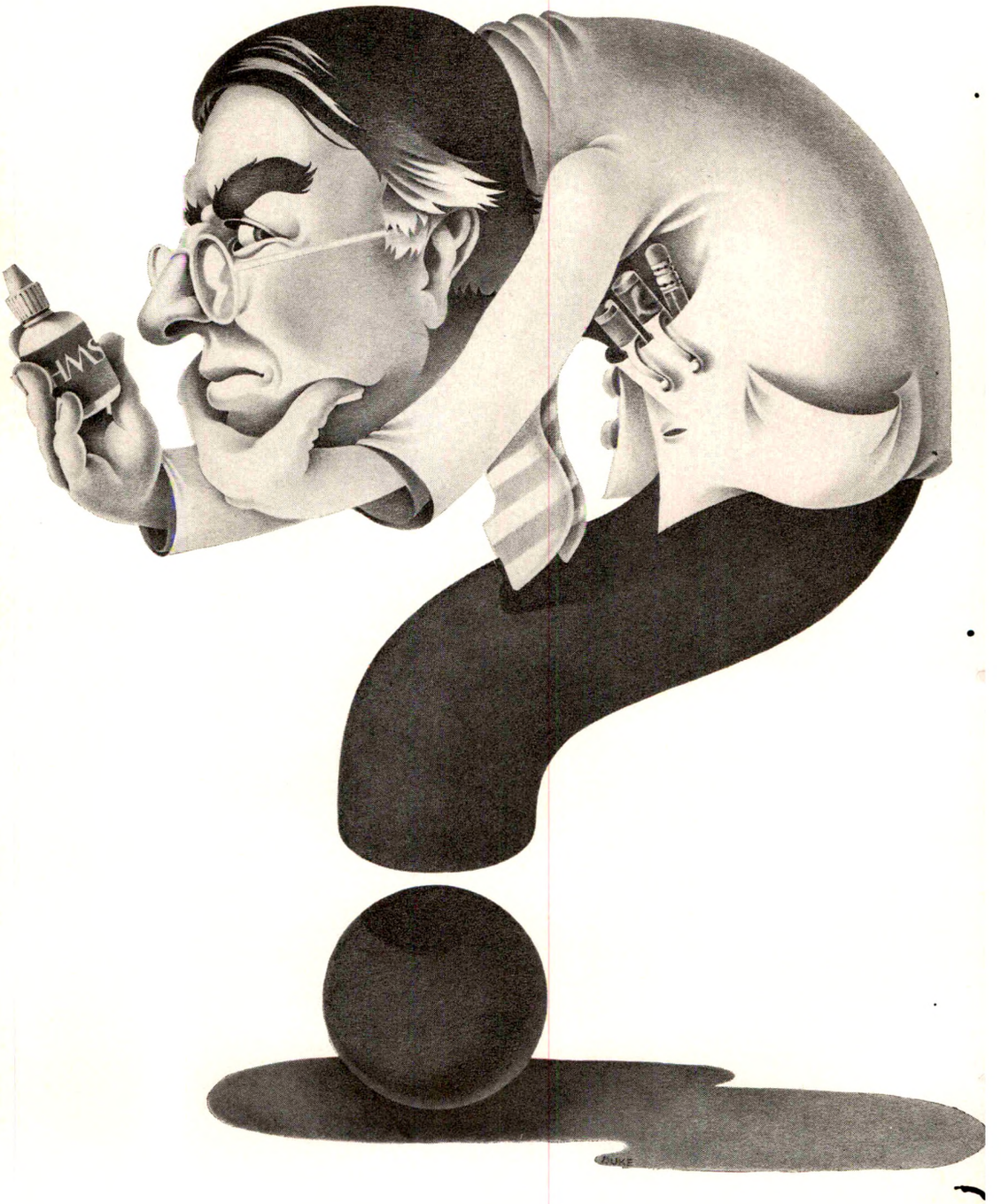
Irvine, California / Montreal, Canada

*Contains:* naphazoline HCl, 0.1%; Liquifilm® (polyvinyl alcohol), 1.4%; with benzalkonium chloride, disodium edetate, citric acid, sodium citrate, sodium chloride, sodium hydroxide and purified water. *Indications:* for use as a vasoconstrictor in conjunctival hyperemic conditions of various etiologies to relieve such symptoms as itching, smarting and redness. *Warnings:* Should not be used in patients with narrow angle glaucoma. If irritation persists or increases, discontinue use. *Dosage and Administration:* one to two drops instilled in each eye every three to four hours or less frequently, as required to relieve symptoms. *How supplied:* Albalon™ is available in 15 cc. plastic dropper bottles on prescription only.

*from an independent study conducted on a controlled population; data on file, Allergan Research Department.

# LAST YEAR W TOLD YOU ABOUT THE "PRESSURE-SPARING" EFFECT OF HMS...

(medrysone)



# ...APPARENTLY YOU WANT TO KNOW MORE.

# SO TAKE THIS NEW LOOK AT HMS.

Drawing on nearly seven years of extensive clinical research experience, let's consider those questions you have asked most frequently.

### "Is HMS too mild to benefit my patients with inflammatory conditions?"

In the past five years, numerous independent studies on HMS (medrysone) have been published including those by Becker, and Thygeson.[1-4] Virtually all have reached the same conclusions: HMS is an effective treatment for superficial ocular inflammations.

Additionally, in a recent survey, 76% of the ophthalmologists interviewed who had tried HMS, found it effective when used for the recommended conditions.[5]

### "What therapeutic possibilities are now open to me, with HMS, that were not available with other mild steroids?"

First, over 30% of the population is likely to respond to steroids with an intermediate to high increase in intraocular pressure; steroid use with these patients must therefore be selective and cautious.[6] With HMS, most of these patients now can safely receive long-term steroid treatment.

Secondly, there are those glaucoma patients who must be treated specifically with epinephrine but are nevertheless sensitive to this drug. With HMS as concomitant therapy, Becker and Kolker reported that there was "sufficient improvement in glaucoma control so as to avoid surgery" by allowing continuation of epinephrine therapy.[7]

### "I haven't seen a rise in IOP with mild steroids. Isn't the real concern with the more potent steroids?"

There is ample evidence that .1% dexamethasone produces significant increases in IOP[1,4,8], and even .12% prednisolone, the mildest of the commercially available ophthalmic steroids, has the potential to increase IOP. Conversely, Doctors Becker and Kolker found in their investigational study that "medrysone (HMS) can be administered to patients four times a day for periods of several months with essentially no elevation of intraocular pressure even in individuals highly susceptible to such elevation."[7]

### "Can I treat uveitis and iritis with HMS?"

It is *not* indicated for these conditions. Its merits should only be judged in those conditions where indicated: allergic and vernal conjunctivitis, episcleritis, and epinephrine sensitivity.

### "Is HMS uncomfortable for the patient to use?"

Results of a recent patient study showed that 96% of those tested found HMS completely comfortable in the eye.[9] Though early batches of the product did cause some minor irritation to the eyes of a few patients, this has not been a recurring problem.

HMS® (medrysone)
LIQUIFILM® OPHTHALMIC SUSPENSION

ALLERGAN

Please see next page for Prescribing Information.

## Prescribing Information for

# HMS®(medrysone)

LIQUIFILM® OPHTHALMIC SUSPENSION

DESCRIPTION: Contains:
medrysone.....1.0%
Liquifilm® (polyvinyl alcohol).....1.4%
with: benzalkonium chloride, disodium edetate, sodium chloride, potassium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, methylcellulose, purified water, and sodium hydroxide or hydrochloric acid if needed to adjust pH. HMS (medrysone) is related structurally more to progesterone than to other available corticosteroids.

INDICATIONS: HMS (medrysone) is effective in the treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis and epinephrine sensitivity. HMS (medrysone) is not indicated in iritis or uveitis as its therapeutic effectiveness has not been demonstrated.

CONTRAINDICATIONS:
HMS (medrysone) is contraindicated in the following conditions:

1. Acute untreated purulent ocular infections.
2. Acute herpes simplex (dendritic) keratitis.
3. Viral diseases of the conjunctiva and cornea.
4. Ocular tuberculosis.
5. Fungal diseases of the eye.
6. Hypersensitivity to any of the components of the drug.

WARNINGS:

1. Infectious diseases of the eye may be masked, enhanced or activated by steroids.
2. Corneal or scleral perforation occasionally has been reported with prolonged use of topical steroids. In high dosage they have been associated with corneal thinning.
3. Prolonged use of topical steroids may increase intraocular pressure although data from 2 uncontrolled studies[4,7] indicate that in patients with increased intraocular pressure and in those susceptible to a rise in intraocular pressure upon application of topical steroids, there is less effect on pressure with HMS than with dexamethasone or betamethasone.
4. Prolonged use of topical corticosteroids may rarely be associated with development of posterior subcapsular cataracts.
5. Systemic absorption and systemic side effects may result with the use of topical steroids.

PRECAUTIONS:

1. HMS (medrysone) is not recommended for use in iritis and uveitis as its therapeutic effectiveness has not been demonstrated in these conditions.
2. With prolonged use of HMS (medrysone) the intraocular pressure and lens should be examined periodically.
3. In persistent corneal ulceration where a steroid has been used, or is in use, fungal infection should be suspected.
4. The use of topical steroids in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother.

ADVERSE REACTIONS: Occasional transient stinging and burning may occur on instillation.

DOSAGE AND ADMINISTRATION: One drop instilled in the conjunctival sac up to every four hours.

SUPPLY:
As a 5 cc. sterile suspension in plastic dropper bottles on prescription only.

NOTE: Bottles filled to one-half capacity for proper drop control. Do not freeze.

REFERENCES:


1. Drance, S.M. and Scott, S.: A Comparison of Action of Dexamethasone and Medrysone on Human Intraocular Pressure. Canad. J. Ophth., 3:159, 1968.
2. Bedrossian, R. H., and Eriksen, S. P.: The Treatment of Ocular Inflammation with Medrysone, Arch. Ophth., 81:184, Feb., 1969.
3. Dorsch, W., and Thygeson, P.: The Clinical Efficacy of Medrysone, A New Ophthalmic Steroid, Amer. J. Ophth., 65:74, Jan. 1968.
4. Spaeth, G. L.: An Anti-Inflammatory Steroid Without Apparent Effect on Intra-Ocular Pressure, Arch. Ophth., 75:783, 1966.
5. Data on file, Allergan Marketing Department.
6. Armaly, M. F.: Factors Affecting the Dose Response Relationship in Steroid-Induced Ocular Hypertension, Chapter VII, Ocular Anti-Inflammatory Therapy, Ed. by H. E. Kaufman, Charles C. Thomas, Springfield, Ill., 1970, pp. 88-97.
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9. Data on file, Allergan Research Department.


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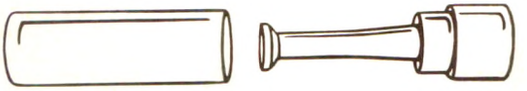
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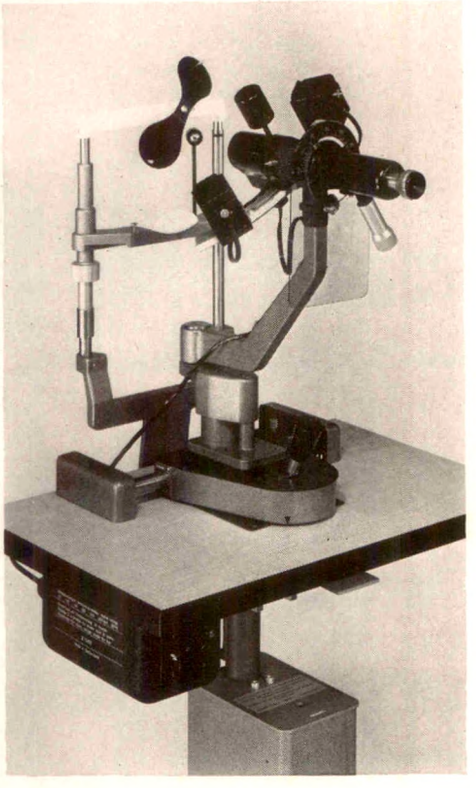
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The Javal-Schiotz Ophthalmometer is in great demand for the fitting of contact lenses. It provides quick and accurate measurements of the corneal radius of curvature, the refractive power, and the direction of the principle meridians. Its range extends from 5.5 to 11 mm., or from 30 to 60 diopters. Two readings—the radius of curvature in millimeters and the refractive power in diopters — can be made on the two graduated scales of the arc. The use of complementary colors, which when superimposed on each other produce white light, enables the observer to focus very accurately. If desired, color glasses can be removed for work with white images.



Unusual luminous fixation point can be easily seen even by patients with poor vision. New dual-purpose "joystick" focusing control simplifies and speeds up positioning of the instrument in all directions.

**H5500-950** — Javal-Schiotz Ophthalmometer on spring-balanced table #1000, with head and chin rest, transformer, 7.5 mm. testing ball, chin rest papers, 10 bulbs 6V, breath shield and cover. . . . . $940.00

**H5500-951** — Javal-Schiotz Ophthalmometer, Unit Model. . . . . $705.00

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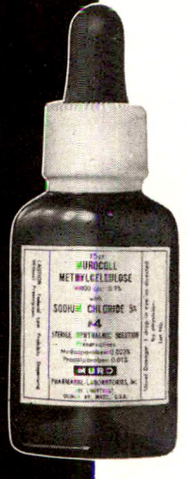

## Muro
## Ointment
## Sodium Chloride 5%

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An ointment of hypertonic sodium chloride solution in a base of lanolin, liquid petrolatum and white petrolatum.

Apply to conjuctiva at bedtime.

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## Murocoll Methylcellulose
## 4000 cps 0.9%
## with Sodium Chloride 5%

*MUROCOLL PRODUCT NO. 4 / SUPPLIED 15cc and 30cc*

A hypertonic solution of sodium chloride with methylcellulose. Preservatives - methylparaben and propylparaben.

TO REDUCE CORNEAL EDEMA: 1 or 2 drops in affected eye 3 times a day or as directed by the physician.

MURO preparations are available to all pharmacies and hospitals through their drug wholesaler.

Complete ophthalmologic formulary available on request.

Federal law prohibits dispensing without prescription.

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**Tillyer Topics**



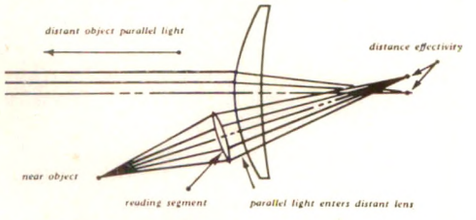
E. WILLIAM TILLYER

# LENSOMETER® lens measuring instrument

The Lensometer is a meter or instrument designed to measure the power of a lens when light enters the lens in parallel rays. It gives the power in dioptric values. The basic optical design of Lensometer instruments is almost fifty years old. But the function and limitations are still often misunderstood.

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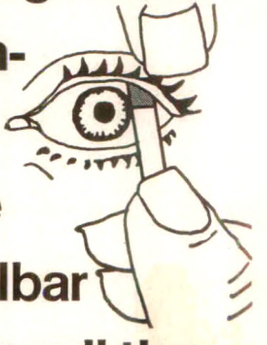
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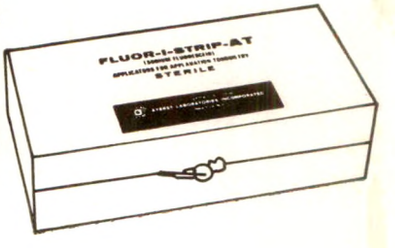


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# Who's Out of Date?

Doctors are increasingly being blamed for not bringing to their patients enough of the benefits of recent medical progress. Overwork, isolation and frank lack of motivation are cited as contributing toward an inability to keep up to date. Rarely is it suggested that a substantial amount of the trouble might be due to our system of medical education.

The fact is, however, that the accelerating accumulation of scientific knowledge has made our style of medical education as out of date as its oldest products, and with less awareness in the universities than in the remotest doctor's office. The amount of information now both available and necessary for proper patient care has grown far beyond the ability of any person to carry in his head. Despite any disclaimers to the contrary, the vast apparatus of American medical education has not accepted that fact and continues with what it perceives as its mission of programming its graduates with sufficient information for a lifetime of practice in some specialty. The chief instrument for enforcing this self-defeating demand for memorization on students and house officers (and the chief evidence of that demand) is our elaborate hierarchal test complex. As presently constituted, the tests given by the National Board of Medical Examiners and all the major specialty boards limit the information a candidate may use to what he carries into the hall in his head. Most medical-school tests do the same thing.

After eight years of such tests it is small wonder that the average graduate adopts a style of practice in which all the information he uses is what he can remember. Yet, as unconscious of what they are doing as the most mindless of L.M.D.'s, medical educators persist in writing the same prescription over and over, ordering bigger and bigger doses of the same medicine, despite the obvious signs that it is not working and the patient has had far too much already.

What are some of the effects of clinging to this outmoded concept of medical education?

The first is on the student. The requirement to commit facts to memory has long been recognized as taking much of the fun out of medical school and to a degree out of residency. Worse than that, it severely limits the scope of what is taught. For example, the amount of factual data that can be memorized for the first part of the National Boards seems not to represent the best possible scientific preparation for a career that will be at its peak in the year 2000. On the wards, patient care and the development of clinical skills and judgment suffer while attending professors deliver extemporaneous board-oriented lectures.

The second effect is on the doctor. Many of our best men pay a terrible personal price in a fore-doomed struggle to "keep up." There are many doctors' wives who will testify that, next to the telephone, it is the stack of unread journals on their husbands' desks that most intrudes on what should be evenings spent in a happy domestic relation. The journals are either being read or worried about, in either case casting a discouraging spell on the evening. Journal reading becomes a joyless exercise, with the reader racing for speed and retention and wondering if he should take a course in speed reading, if only he could find the time for it.

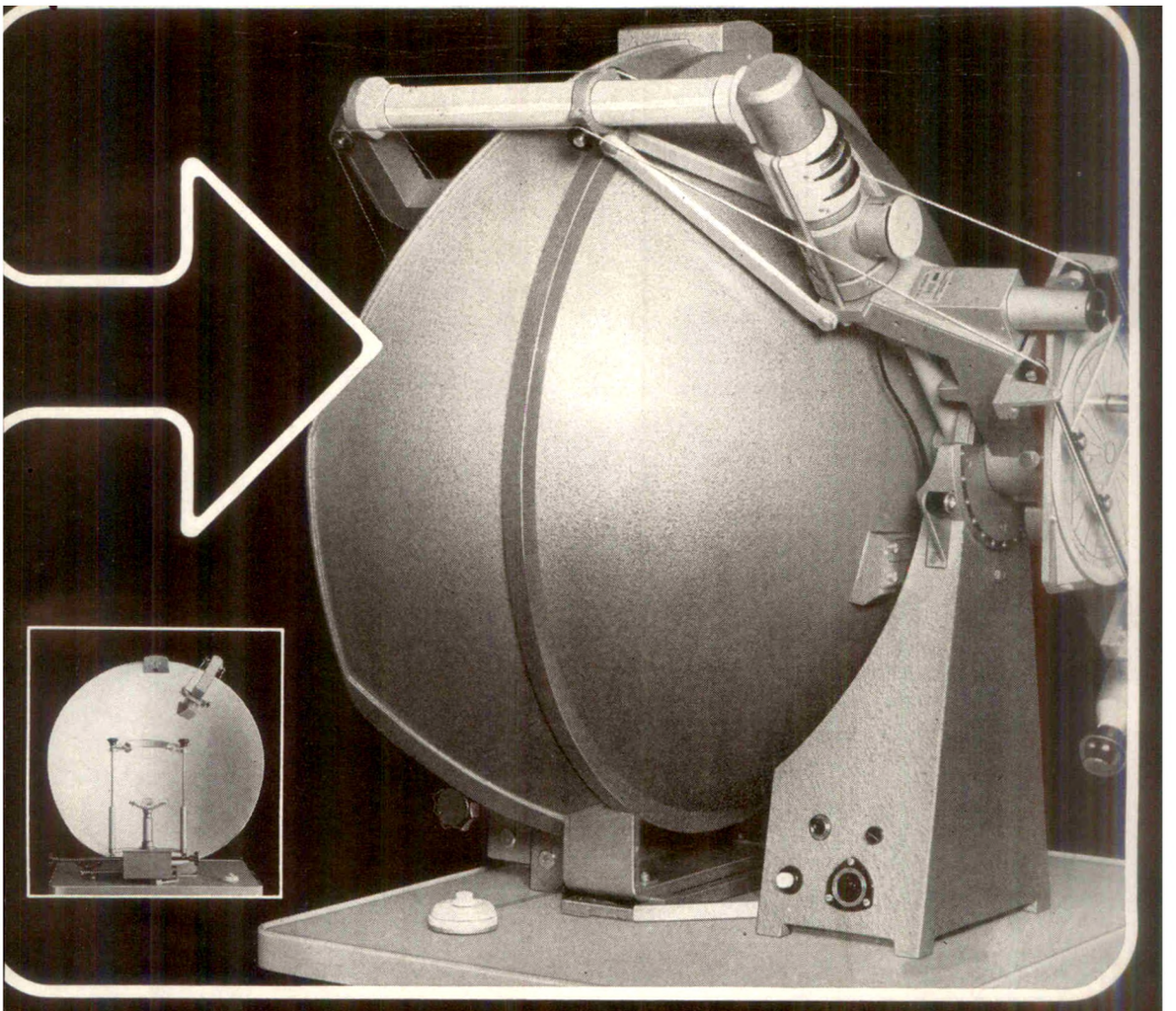
Finally, and most importantly, is the effect on the problem patient and his chances of getting the best possible care. An enlightening study* of a doctor's day clocked the minute-by-minute activities of 20 internists and general practitioners. There was not a single notation suggesting that any one of the 20 stopped to look up anything pertaining to any one of the patients he saw during an entire week. Clearly, some patients were being shortchanged.

If we are to train doctors who will do better than this, we must shift our emphasis toward the skillful obtaining of information rather than on its retention. The whole fabric of medical education must be altered to emphasize that different orientation. One of the first things to be changed must obviously be the tests. Most written tests, including those of the specialty boards, could well be taken to the library before being returned. The passing grade might be moved close to 100 per cent, and candidates given two or three chances to pass. Oral examinations could be similarly modified to allow the candidate an appropriate search for information. Instruction should be at more basic levels than at present and designed to help promote a critical understanding of specific articles. There should be further emphasis on training the student to develop judgment in when to turn to the library for help, skill in using available sources of information and retrieval, and a discriminatory critical taste in reading the medical literature.

Graduates of such a system should do much better than present ones in making effective use of the information that will come to be available at an increasing rate over their lifetimes.

E. William Rosenberg, M.D.
New England J. Med. 284:850, 1971

* Brody BL, Stokes J III: Use of professional time by internists and general practitioners in group and solo practice. Ann Intern Med 73:741-749, 1970



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# THE STRUCTURE AND FUNCTION OF EXTRAOCULAR MUSCLE— AN APPRAISAL OF THE DUALITY CONCEPT

THE GIFFORD MEMORIAL LECTURE*

GOODWIN M. BREININ, M.D.

*New York, New York*

Ophthalmic physiologists have long been intrigued by the observation that the different types of eye movement have characteristically different time courses ranging from the extremely rapid to the very slow.[1] Fast saccadic, or version (phasic) movements may reach a speed of 400-600 degrees per second, requiring only milliseconds for completion, while slow vergence (tonic) movements in the order of 10-20 degrees per second may require up to a second for completion. This duality of function has led to the postulation of an underlying dual anatomic and physiologic mechanism described in a landmark paper by Hess and Pilar,[2] 1963. Considerable evidence has been adduced from anatomic, pharmacologic, and physiologic studies to support this concept. Rapidly proliferating experimental data, however, now indicate a vastly more complex organization than was initially thought to be the case. The suggestion that a system involving both somatic and autonomic elements accounts for the rapid and the slow movements respectively (Alpern and Wolter,[1] 1956) has not been substantiated.

From the Department of Ophthalmology, New York University School of Medicine. This study was supported in part by Grants EY00191-13 and EY00309-05 from the National Eye Institute.

* Presented before the Chicago Ophthalmological Society on May 22, 1970.

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## ANATOMY

Extraocular muscle of man and most animals contains both extrafusal (motor) fibers and intrafusal (spindle) fibers. The latter have not been seen in extraocular muscle of rabbit, cat, and dog but do occur in primates.

The organization of extraocular muscle into small-diameter and large-diameter extrafusal muscle fibers has long been known (Kato,[3] 1938). On the basis of fiber histology the former have been called "felderstruktur," and the latter "fibrillenstruktur" in the terminology of Kruger,[4] 1949, and Kruger and Gunther,[5] 1955. Felderstruktur refers to the fieldlike appearance of the small fiber in cross section with poor, irregular demarcation and separation of the myofibrils by the very scanty sarcoplasmic reticulum. The fiber is considered to be slow or tonic. Fibrillenstruktur refers to the fibrillar appearance of the large fiber in cross section with well-demarcated myofibrils surrounded by an abundant sleeve of sarcoplasmic reticulum. This is the typical twitch or fast fiber. The slow fiber has been most extensively studied in the frog "tonus bundle." Kruger's terminology has proved popular although with increasing information (Zenker and Anzenbacher,[6] 1964), the distinction between the two types begins to blur.

The earliest physiologic studies of the two fiber types were also carried out in amphibia —by Tasaki & Mizutani,[7] 1944, in the toad, and by Kuffler and Vaughan Williams,[8,9]

1953, in frog iliofibularis. The twitch fiber of extraocular muscle closely resembles the twitch fiber of skeletal muscle. It receives innervation from large diameter motor nerves (alpha range) and exhibits one or two motor end plates resembling the "en plaque" ending with many post-junctional folds. The tonic fiber of extraocular muscle has no counterpart in the peripheral skeletal musculature of mammals although it is also present in the stapedius and tensor tympani muscles of the middle ear. It bears resemblance to the tonic fiber of the frog. It receives innervation from small-diameter motor nerves (gamma spectrum) and exhibits nerve endings distributed along its length resembling the multiple "en grappe" endings. These lie in apposition to the sarcolemma with few or no post-junctional folds. There is good evidence that muscle fibers with distributed innervation receive nerve fibers from more than one nerve cell (polyneuronal), a quite unique situation giving rise to the possibility of a variety of methods of control and response. The exact locations and relations within the ocular motor nuclei of the cell bodies of nerves supplying twitch and slow (tonic) fibers are not yet known.

The typical twitch muscle fiber has a well delineated transverse tubular system which in association with two terminal cysterns of the longitudinal sarcoplasmic reticulum forms characteristic triads. These triads are located at the junction of the A and I bands of the sarcomere in mammals. The transverse tubule is in continuity with the surface membrane (sarcolemma) and provides a conductive pathway for the nerve action current from the fiber surface into its interior. In this way, depolarization activates the rapid excitation-contraction coupling mechanism with calcium release from the sarcoplasmic reticulum to the myofibril and its recapture by the sarcoplasmic reticulum during the repolarization phase. The actual contraction of the fiber presumably occurs by the sliding of the thin actin past the thick myosin filaments within the sarcomeres through the formation of reversible chemical bonds or bridges (sliding filament theory).

The tonic muscle fiber has few or no triads and only a rudimentary transverse tubular system. The excitation-contraction mechanism, therefore, lacks the physical basis for rapid muscle contraction. The distributed innervation is necessary for contraction of the whole fiber which occurs slowly and segmentally rather than in the rapid, all or none manner of the twitch fiber. The most recent studies of extraocular muscle suggest that between the typical twitch and slow fibers occur three other fiber types intermediate in structure, enzyme profiles and presumably function (Peachey,[10] 1969).

## Ultrastructure

Reports on the ultrastructure of extraocular muscle are in close agreement concerning some fibers but at striking variance with respect to others. In a recent conference, Peachey,[10] 1969, reviewed the literature and attempted a synthesis of these conflicting and confusing findings.

He criticized the concept that the muscle fibers run the whole length of the muscle. If they do not, then transverse sections of the muscle could show marked differences depending on the level of section (vide infra). It is also clear that there is a considerable species variation so that the fiber characteristics of rabbit, cat, dog or monkey do not correspond precisely with each other or with man. In addition, there is variability among the extraocular muscles themselves. Thus the ultrastructure of superior oblique differs from rectus and even inferior oblique. It has been noted that the levator and retractor bulbi appear to contain only twitch fibers.

It is generally agreed that a layer of small fibers invests the orbital surface of the muscle. The small fibers, however, also occur throughout the thickness of the muscle. Kern,[11] 1965, recorded in vitro acetylcholine contracture of the orbital surface layer of tonic fibers which could be readily separated in the rabbit. Miller,[12] in 1967, found the sur-

face layer to correspond with red muscle by histochemistry and its heavy content of mitochondria. He defined the central muscle mass by these criteria as white. His assumption that the surface layer is responsible for vergence and fixation while the center is used for following and saccadic movement, while intriguing, cannot be accepted as fact for reasons which will be presented later.

The structural definitions of twitch and slow fiber have been steadily changing. The large fibers which show abundant sarcoplasmic reticulum discretely separating the myofibrils; with regular, regimented Z lines; with clear-cut triads at the A-I interface of the sacromere; with well-delineated M lines, singly innervated with only one or two en plaque type endings showing numerous post-junctional folds, are accepted as twitch, fast, fibrillenstruktur fibers. The small fibers exhibiting scant sarcoplasmic reticulum with coalescent, poorly separated myofibrils; with wavy, irregular, poorly registered Z lines; with few or no triads; with absent M lines; with multiply innervated en grappe type endings showing few or no post-junctional folds are accepted as slow, tonic, felderstruktur fibers. The typical slow fiber may have heavy accumulations of mitochondria and demonstrate abundant succinic dehydrogenase enzyme activity indicating an extensive oxidative metabolism characteristic of slowly contracting muscle. The typical twitch fiber has a scanty mitochondrial concentration and an enzyme profile indicating a glycolytic metabolism characteristic of rapidly contracting muscle. Nevertheless, marked variations of morphology, mitochondrial and enzyme distribution have been reported in the extraocular muscle fibers.

After reviewing the literature, Peachey[10] has delineated five fiber types—two on the orbital surface of the muscle and three in the interior. These vary from the typical twitch and slow to markedly atypical fibers. He cautions against the easy acceptance of such terms as fast and slow; fibrillenstruktur and felderstruktur, en plaque and en grappe. That the extraocular slow fiber is indeed analogous to the frog slow fiber is in question as well as the entire present correlation of structure and function. The presence or absence of M lines may turn out to be related to fixation technique; innervation pattern (single or multiple) may also prove an unreliable criterion; fiber size is also unreliable since some fibrillen-type fibers are smaller than some felder-type fibers. Nevertheless, until more precise information and analysis is available we may be forgiven for persisting in the use of these terms for heuristic and practical reasons.

In our laboratories, Davidowitz has recently devised a method for correlating the fine structure of longitudinal and transverse sections of given extraocular muscle fibers. Specific cells may be preselected for this purpose from serial cross-sections of the entire muscle, thus making it possible to repeatedly examine the same fiber along its length.

Preliminary findings indicate that the detection of all fiber types within an extraocular muscle may require that one sample that muscle thoroughly along its length, insofar as the distribution of fiber types and their layering apparently varies considerably from origin to insertion. Even the orbital surface layer of small-diameter cells may be seen to subdivide into two layers of different fiber diameter at some portions of the muscle, while elsewhere along the surface only one or neither of these populations may appear.

If these observations are sustained it will help explain the varying reports in the literature. Of interest is a recent report by Floyd,[13] in 1970, of a previously undescribed cholinesterase-staining muscle-fiber-muscle-fiber junction in cat extraocular muscle. This adds to the complexity of fiber relationships and raises many questions of fiber function.

## Pharmacology and physiology

The pharmacologic responses of extraocular muscle have long been of great interest. Frequently cited is the unusual sensitiv-

ity of this muscle to acetylcholine, choline, and nicotine (Duke-Elder and Duke-Elder,[14] 1930, Brown and Harvey,[15] 1941). It has been shown by Breinin and Perryman,[16] 1964, that the enhanced chemical sensitivity of extraocular muscle over peripheral skeletal muscle does not hold up with the exception of the phenomenon of contracture—the sustained contraction of the muscle fiber in the absence of muscle action potentials. Drug-induced contracture constitutes a major distinction between these muscle types and has been stated to depend upon the slow, multiply innervated fibers (Kern[11] 1965) which tend to be concentrated in the outermost (orbital) surface of the extraocular muscle. The phenomenon is best seen after the use of succinylcholine, which depolarizes the muscle fibers, presumably engendering a flaccid paralysis of the twitch fiber and a contracture of the slow fiber. Contracture may produce up to one-third of the maximal tetanic tension (Bach-y-Rita and Ito,[17] 1966, Eakins and Katz,[18] 1966). Lacking the slow fiber, peripheral skeletal muscle does not show contracture to a comparable drug concentration.

It has been reported that the extraocular muscles contract with epinephrine (Eakins and Katz,[18,19] 1966-7, Sanghvi,[20] 1967). This is a debatable point, conflicting with other reports (Breinin and Perryman,[16] 1964). Neither stimulation nor paralysis of the cervical sympathetic neural chain induced or altered the response of the extraocular muscle (Brecher and Mitchell[21] 1957, Van Allen and Blodi,[22] 1960). It seems doubtful that epinephrine is a physiologic stimulant of extraocular muscle, although it may exert indirect effects producing weak contraction. The responses of extraocular muscle to cholinomimetics have been reported recently by Sanghvi and Smith,[23] 1969. They believe that the drug-induced activation of mixed muscle systems (twitch and slow) may be due to direct depolarization and contracture plus propagated membrane depolarization consequent to a drug-induced effect post- or presynaptically. The contribution of each of these routes of activation is a function of dose of the stimulant. They also found, surprisingly, that the eye muscles are less sensitive to tubocurarine than limb muscles and suggest that the slow fibers are more sensitive than the twitch fibers. These observations, however, are at variance with clinical experience in man. The authors point out morphologic, physiologic, and pharmacologic similarities of the slow muscle fiber and the slow intrafusal spindle fibers of cat.

The ability of extraocular muscle to contract very quickly reflects its organization into small innervation ratio units resulting in a very brief twitch and a high tetanus fusion frequency. The twitch time of 5-8 msec (Cooper and Eccles,[24] 1930) and the high fusion frequency (400-600°) appear based on the fast twitch fiber. The classic slow fiber has a much longer rise time (20-27 msec) and a long decay (up to 200 msec) (Bach-y-Rita and Ito,[17] 1966). It produces prolonged segmental, graded contractions rather than twitches and has a very low fusion frequency (15-25). The controversial "slow, multiply innervated twitch fiber" presumably produces an intermediate speed contraction.

The existence of a fast and slow response system in extraocular muscle of the cat was most convincingly shown by Hess and Pilar[2] in 1963. They patterned their experiments on the studies in frog by Kuffler and Vaughn Williams,[8,9] 1953, which conclusively demonstrated the existence of slow and fast nerve and muscle fibers. Tasaki and Mizutani,[7] 1944, had previously demonstrated the dual response in the toad. The fast fiber in the frog corresponds with the usual twitch skeletal muscle fiber. The slow fiber is unique and is found in muscles subserving amplexus, the prolonged grasping of male and female frogs during mating. The fibers differ in membrane potential, end-plate, and miniature end-plate potentials and particularly

in the existence of typical all-or-none, propagated action potentials (spikes) in the twitch fiber whereas only multiple, non-propagated, small junctional potentials occur in the slow fiber. The twitch fiber shows the usual non-graded contraction, whereas the slow fiber exhibits graded contractions. Hess and Pilar,[2] in 1963, used intracellular microelectrode techniques to characterize the electrophysiologic properties of the two fiber types in cat extraocular muscle. They also determined the innervation pattern and histology by both light and electron microscopy.

They found that one fiber group (twitch) had propagated action potentials averaging 80 mv. These cells had resting potentials averaging 65 mv. The end-plate potential had a rise time of 2-3 msec. A second fiber group (slow) had complex non-propagated potentials of much smaller amplitude (12-14 mv) arising from multiple sites within the fiber and exhibiting a polyneuronal origin. The membrane potential of these cells averaged 45 mv.

Miniature junctional potentials were recorded from both groups of fibers and showed a longer duration and higher amplitude in the slow fiber.

Bach-y-Rita and Ito,[17] 1966, carried out a similar study on the cat. The principal difference lay in their report that slow fibers were also able to produce propagated action currents (spikes) when suitably stimulated. In fact, the authors stress the existence of the "slow, multiply innervated twitch fiber." This has become a central point of controversy since it indicates loss of distinction between the two groups. The fiber groups, however, were differentiable by impulse conduction velocities, range of membrane potentials, amplitudes and frequencies of miniature end-plate potentials, responses to succinylcholine, frequency of stimulation required for tetanus, and by velocities of conduction of the nerve fibers innervating each of the muscle fiber types.

The existence of tonic and phasic fibers in extraocular muscle of rabbit was actually first shown by Matyushkin,[25] 1961. He clearly recorded typical fast action potentials by stimulation of phasic fibers and the slow, non-propagated potentials occurring spontaneously in tonic fibers. Similar findings in rabbit were obtained by Ozawa,[26] in 1964. Both described the occurrence of spontaneous potentials only in slow fibers, an observation of paramount interest. This correlates with reports that only small nerve fibers and related central cell bodies show spontaneous activity, whereas large-diameter nerve fibers and their central connections are silent until eye movement is called for. This has led to the inference that the constant tonic activity characteristic of the electromyogram (EMG) of extraocular muscle is a product of the slow motor system exclusively. It has also been proposed that saccadic movement is a property solely of the fast motor system whereas vergences, fixation, and pursuit movements are attributable to the slow system. The importance of these concepts to clinical ophthalmology is self-evident, but they are far too simplistic and do not fully accord with the facts.

A precise interpretation of the normal EMG of extraocular muscle still eludes us. The motor unit activity of tonic firing clearly consists of propagated spikes. These could not arise from non-propagated junctional potentials and could not be a product of the slow system unless we accept Bach-y-Rita and Ito's postulation of the slow, multi-innervated twitch fibers; hence the importance of establishing the existence and role of such spike producing slow fibers. Studies of ocular kinesiology have not shown an exclusive role for either twitch or slow fibers—in fact, both systems appear implicated in all movements but may differ in the degree to which they are involved. It seems reasonable to suppose that the fast system plays the predominant role in saccades, whereas the slow system is primarily involved in vergence, fixation, and perhaps pursuit, providing the

sustained and steadying features of such movements. The seductive charm of this reasoning, however, must not lead us to premature conclusions. Nothing is yet established in fact. These considerations have led to more rigorous efforts to establish the electrophysiologic characteristics of the slow fiber system. Pilar,[27] 1967, analyzed electrical and mechanical responses of the cat superior oblique slow fiber. He convincingly demonstrated that under a variety of conditions the slow fibers respond with graded contractions and without propagated overshoot potentials. He pointed out sources of error in Bach-y-Rita and Ito's arguments for the slow, multiply innervated twitch fiber. The classic slow and fast systems are given strong support by his paper. Ozawa, Cheng, Davidowitz, and Breinin,[28] 1969, reported a combined physiologic and morphologic study of potentials and fiber type in extraocular muscle. EMG potentials were recorded simultaneously with spontaneous intracellular multifocus slow potentials, using computer and optical techniques. EMG potentials clearly synchronous with the spontaneous intracellular potentials were found to be monophasic and at least 4 msec in duration—clearly different than spike potentials. After recording such potentials the same fibers were intracellularly stained with the dye-fast green injected through the recording micro-electrode; the marked fibers were then stained for innervation type by cholinesterase stain. A positive correlation of slow potential with the multiply innervated fiber was obtained. The recorded potentials closely resembled those obtained by Matyushkin,[29] 1964, and Nemet and Miller,[30] 1968, and interpreted by them as arising in slow fibers. A similar correlation has been obtained in spike-producing, singly innervated fibers.

In a series of experiments[28] determining membrane potential, the occurrence of spontaneous potentials, the ability to produce overshoot spikes by stimulation, and the correlation with fiber type through fiber marking with fast green and cholinesterase stain for innervation pattern, it was found that an overshoot spike potential was obtained in two "silent" fibers of multiply innervated type. Of 53 fibers producing spontaneous, slow, multifocus potentials, none could be stimulated to produce action potentials. An additional 23 "silent" fibers in which spike potentials could be evoked were found to be singly innervated.

In reviewing electromyograms of extraocular muscle, many traces have been obtained showing long duration, monophasic waves. These were originally misinterpreted as "envelopes" owing to the remoteness of the electrode from active muscle fibers. On further probing of the muscle, areas of spiking activity were usually obtained. In some muscles no spiking activity at all was encountered. Under general anesthesia spike activity is rare whereas traces of slow monophasic activity are frequently obtained. These appear reasonably to be of slow fiber origin. In decerebrate cat experiments the extracellular electrode was applied to the extraocular muscle surface by means of a manipulator. Frequently, one obtained pure slow activity consisting of long-duration monophasic waves. With gradual penetration, layer by layer, the activity shifted to spikes. On reversal of direction, the surface slow activity was again encountered. This suggests that it is entirely possible to record classic slow activity in the extracellular EMG electrode (Breinin, unpublished observations.)

The question still remains unanswered whether spike activity may also reflect the slow motor system. Until this point is resolved it will be difficult to ascribe a given movement to a specific fiber type or system.

It is tempting to speculate but premature to aver the existence of a differential pathology involving the fiber systems. Is strabismus attributable to a derangement of one or the other systems or to an imbalance between them? Are neuromotility disorders related to

specific defects in fiber mechanisms? Is there a differential susceptibility of fast and slow fibers to various pathologic agents and conditions? If such fiber-specific pathology does exist, it may lead to a differential therapy and hence to a more rational etiologic and therapeutic approach to extraocular muscle disorders.

### Bio-engineering

The increasing application of engineering principles to the oculomotor system has been most productive. The dynamics of extraocular muscle have been extensively investigated by Robinson[31-33] 1964-69, employing the classic approaches of muscle force–velocity and length–tension plots and by study of the nature of orbital resistance. From these studies it is possible to formulate muscle models and to speculate on the servo-systems which govern eye movement. Although still in their infancy, these investigations have led to valuable insights in both normal and abnormal oculomotor physiology.

Robinson has analyzed the mechanics of ocular saccadic, smooth pursuit, and vergence movement in man. His findings are summarized as follows along with some comments and criticisms.

1. The eye is impulsively driven in a saccade by a brief burst of force much larger than that needed to hold the eye in its new position.

2. The mass of the eyeball plays a negligible role in determining the time course of the saccade.

3. There is no active checking. The eyeball is decelerated by the highly viscous nature of the orbital supporting structures.

The last conclusion is evident in EMG traces of saccadic movement which show an abrupt inhibition of the agonist at the termination of a saccade without any preceding checking action by the antagonist. The saccade is thus ballistiform in nature. It is extraordinary that the viscous orbital resistance, including that of the muscles themselves, is sufficient to stop high-velocity saccades with minimal overshoot—almost as though the globe hits a stone wall.

4. Larger saccades are achieved by increasing the duration of the excess force applied since the intensity of the force, although large, is limited. In engineering parlance this is termed frequency compensation (or neural pre-emphasis).

5. Smooth pursuit movements are markedly different than saccadic and exhibit quite different mechanical parameters.

This evidence is adduced for separate and independent control systems. There is no basis, however, for assuming that separate fiber types are involved. Typical spike EMG traces correlate closely with a given movement. There is no evidence of classic slow fiber activity unless we accept Bach-y-Rita and Ito's postulation of slow, multi-innervated twitch fibers.

6. Vergence movements, on the other hand, show a slow rise of tension compared with other movements. The time course of vergence movements suggests a very different neuromuscular control mechanism and leads to the implication of the slow fiber system.

The evidence of tension (Robinson[34]) and EMG (Miller,[35] 1958) studies indicate that the peak of tension may outlast the peak of recorded electrical activity. This lack of correlation is the basis of the suggestion that a fiber system not recorded in the EMG is active—presumably of slow motor type. There are many sources for error in this suggestion. The EMG electrode may not have been placed suitably with respect to the active units and hence did not record them, as Robinson notes. The fact that some units may have a specific field of action and thus not be commensurate with tension; has also been known for many years. But the fact that classic slow fibers can be recorded in the EMG is of fundamental importance and these have not yet been demonstrated in vergence studies. That the slow, multi-inner-

vated twitch fibers postulated by Bach-y-Rita and Ito are responsible for the slow time course of vergence awaits demonstration. It appears reasonable that both slow and twitch fibers operate in vergence but to differing extents.

## Conclusion

The attempt to correlate specific fiber types and function is at present bogged down in uncertainty. We do not know how many different fiber types actually exist. The early exposition of two fiber types, fast and slow, is being discarded in favor of three, five or more fiber types. Indeed, there may be a whole spectrum or continuum of fibers ranging from slow to intermediate to fast. The histologic criteria of separateness are beginning to break down so that we do not know what exactly constitutes a slow fiber. Still less can we ascribe a specific function to a specific fiber type. It is clear that motor systems of very different organization participate to differing extents in the various eye movements. Attempts to unravel the puzzle will require much more work at both the functional and structural levels, including the central nervous system and the peripheral effector mechanism. Despite its oversimplification, we must pay tribute to the dual-fiber concept which has led to the most astonishing worldwide development of interest in the oculomotor system by physiologists, anatomists, and ophthalmologists. From burgeoning laboratory and clinical studies we are gaining a fascinating understanding and appreciation of the complexity, diversity, and utility of the visuomotor mechanism. It is reasonable to hope that these studies will lead to significant clinical advances in strabismus and neuromotility disorders.

We also see in the slow motor mechanism a possible link between amplexus in the frog and vergence in man—another example of nature eternally adapting structure to function, preserving in the more complex organisms those modifications which serve the purpose and have withstood the test of time.

## Summary

The structure and function of extraocular muscle is analyzed in terms of the duality concept, which defines a slow and a fast motor system based upon slow and fast muscle fibers. The anatomical characteristics of the slow and fast motor system, including muscle and nerve, are reviewed with respect to light and electron microscopic structure. The pharmacology and physiology of extraocular muscle are reviewed with respect to the special properties of the slow and fast muscle fibers and their innervation. After consideration of the role of the slow and fast motor system in the electromyelogram, and finally, bio-engineering aspects of ocular movement in terms of the slow and fast motor systems, it is concluded that there is insufficient evidence to ascribe specific functions to specific muscle fibers. It is probable that eye movements are based upon coordinated and integrated action of both slow and fast motor systems. The consideration of oculomotor function as manifestation of either a slow or a fast motor system is an oversimplification, but this concept is proving helpful in stimulating research in normal and abnormal eye movement.

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# LIMITATIONS OF COVER TEST IN DETECTING STRABISMUS

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The cover test—the placing of a cover before one eye and observing the fellow eye for a refixation movement—is of fundamental value in the diagnosis of manifest strabismus. Recently, several ultra-small-angle types of strabismus have been described.[1-3] In these conditions, the cover test is essential to both definition and diagnosis. Also, the absence of a shift on the cover test has been said to indicate the absence of strabismus,[4] the presence of binocular single vision,[5,6] and bifoveal fixation.[7,8]

The smallest shift detectable with the cover test has been estimated to be from one to four diopters.[9-11] Ludvigh[12] concluded that excursions of less than 1 to 2 prism diopters could not be reliably perceived by the unaided eye. He arrived at this conclusion by having several examiners individually observe the eyes of one subject who performed voluntary fixation movements of known amplitude after a signal by the examiner.

In view of the scarcity of comparable experimental data and the renewed emphasis being placed on the cover test, we have undertaken the present study in order to define the limits of this test.

## METHOD

Ten experienced examiners with normal vision were tested for their ability to detect small saccadic refixation eye movements as elicited by the cover test. They included four orthoptists, two senior ophthalmology residents, two post-residency ophthalmology fellows, and the authors.

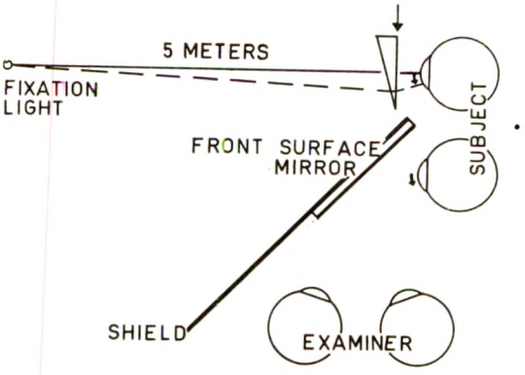



Fig. 1 (Romano and von Noorden). Experimental method. Simulation of cover test in clinical use. A small reflex refixation eye movement is induced by a prism while the examiner attempts to detect and describe it.

Each individual served as an examiner, and then as the subject for a subsequent examiner. The experimental arrangement is illustrated in Figure 1. The subject's right eye fixated a light at five meters. Prisms were placed, base-out or base-in, one at a time, before the right eye. This induced a small conjugate refixation movement. The examiner observed the left eye of the subject through a front surface mirror. The front surface mirror and shield prevented any fusional movements of the subject's eyes. It also prevented the examiner from observing the time or method of induction of eye movements.

The examiner was requested to indicate when the eye had moved and also the direction of the movement. Prisms of four, three, two, one, and one-half prism diopter's power were presented singly in a statistically deter-

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TABLE 1

RESULTS IN AN EVALUATON OF THE COVER TEST—NUMBER OF ERRORS IN 20 TRIALS AT EACH MAGNITUDE OF EYE MOVEMENT

| Eye Movement | Examiner | | | | | | | | | | Average Errors |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |
| Four ΔD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Three ΔD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Two ΔD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| One ΔD | 0 | 0 | 3 | 5 | 0 | 4 | 0 | 14 | 6 | 4 | 3.6 |
| One-half ΔD | 4 | 7 | 5 | 20 | 9 | 13 | 4 | 18 | 6 | 16 | 10.2 |

mined random order. For a control, a rectangular piece of glass without prismatic power was inserted before the subject's eye at random intervals. With 20 trials of each of the five prism sizes, a total of 100 possible eye movements was presented to each examiner.

## RESULTS

The results are shown in Table 1. All 10 examiners made no error in detecting movements of two prism diopters or more. For movements of one prism diopter, the average was 3.6 errors in 20 trials; for movements of one-half prism diopter, the average was over 10 errors in 20 trials.

At the 95% probability level, our experienced examiners were, individually and as a group, unreliable in detecting movements of one-half prism diopter. For movements of one prism diopter, the group was still not reliable at that probability level, although several individual examiners were. All examiners were, with no exception, reliable in the detection of movements of two prism diopters or more. The best scores (examiners 1 and 7) were achieved by an orthoptist in training and by an ophthalmology resident.

## DISCUSSION

In spite of differences in experimental technique, our results agree closely with those obtained by Ludvigh.[12] Of the 11 examiners in his series, Ludvigh found none reliable at one-half prism diopter, eight reliable at one prism diopter, and three at two prism diopters. As a group, his examiners, like ours, were reliable only in detecting movements of two prism diopters or more.

Therefore, we concur with Ludvigh and recommend that two prism diopters be considered the smallest deviation routinely detectable by the cover test. A more conservative limit may be appropriate considering ordinary examining conditions.

We wish to emphasize that the absence of a detectable shift on the cover test means only that a deviation, if present, is probably less than two prism diopters. A negative result on the cover test does not necessarily rule out strabismus, nor does it imply that normal binocular single vision or bifoveal fixation is present. For instance, the cover test will be negative in cases of microstrabismus with parafoveal fixation and identity between the degree of eccentricity of fixation under monocular, and the angle of anomaly under binocular conditions.[3]

What, then, should be done to close this gap in our clinical testing abilities? We find ourselves in agreement with Ludvigh's[12] conclusions of over 20 years ago in this regard: "... either a subjective test should be employed or the examiner should use magnification." The latter should improve the level at which reliable results could be obtained. It would not, however, aid in detection of those forms of microstrabismus in which no movement of the deviated eye occurs on covering the fixating eye.

Of better value in such situations are tests that indicate the degree of binocular cooper-

ation. For this purpose, we recommend the four-diopter prism test[13-14] and tests for stereoacuity.[15]

## Summary

Ten experienced examiners attempted to detect small monocular refixation eye movements, simulating the ordinary clinical use of the cover test. Reflex refixation movements were induced in the observed eye by placing prisms ranging from one-half to four prism diopters before the opposite fixating eye. A shield prevented fusion and the observation of movement induction by the examiner. Although several individual examiners were better, the group as a whole could detect only movements of two prism diopters or more with statistical reliability at the 95% level. The cover test, therefore, is considered unreliable for detecting deviations of less than two prism diopters. The absence of a detectable shift on the cover test does not rule out strabismus or establish the presence of normal binocular single vision or bifoveal fixation.

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# THE PATHOGENESIS OF RETINAL DYSPLASIA

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The term retinal dysplasia has been employed with two connotations in the ophthalmic literature. Its early use[1,2] was the more general, referring to abnormalities in the histogenesis of the developing retina. The term was used more restrictively by Reese and Blodi[3] and Reese and Straatsma[4] to designate a specific syndrome consisting of multiple congenital anomalies, including bilateral ocular abnormalities, presenting a more or less typical histopathologic picture. The widespread application of karyologic analysis during the past decade has made it clear that most of the cases of this syndrome described by Reese and coworkers[3,4] were probably related to a trisomy in the D group of chromosomes (13-15 trisomy).[5-9]

In their description of unilateral retinal dysplasia cases, Hunter and Zimmerman[10] objected to use of the term retinal dysplasia to describe the clinical syndrome, and preferred to restrict its use to the designation of a retinal lesion. They point out that dysplastic retina may be found in a number of different types of eye abnormalities, with or without systemic anomalies, and either unilaterally or bilaterally. They, and other authors, agree that dysplastic development of the retina may result from a wide variety of non-hereditary causes, and more recently Ricci[8] has extended the list of genetic contributions to this pathologic condition.

There are generally, however, only a limited number of pathogenetic mechanisms whereby a specific tissue change within the body may be effected. A review of the retinal dysplasia cases at the Armed Forces Institute of Pathology and at The Johns Hopkins Hospital suggests that all of the cases may conveniently be subdivided into four categories. The first three are as follows: (1) those resulting from hyperplastic extension of the retina into "abnormal" sites away from its pigment epithelium, (2) those secondary to detachment of the retina from the pigment epithelium, and (3) those occurring in an otherwise normal location over areas devoid of pigment epithelium such as occur in colobomas. It will be obvious that the underlying feature in each of these dysplastic processes is the suggested importance of the retinal pigment epithelium as the organizing factor primarily responsible for the normal histogenesis of the retina during development.[10] But another category exists also: (4) an in situ dysplastic process which may involve the entire retina or only a small portion thereof, and in which there is no evidence that the dysplastic retina has ever been separated from its underlying pigment epithelium.

It is the purpose of this paper to illustrate these four types of retinal dysplasia and to discuss their pathogenetic implications.

## MATERIALS AND METHODS

Our survey included an examination of all cases diagnosed as retinal dysplasia in the files of the Eye Pathology Laboratory of The Johns Hopkins Hospital as well as a reexamination of all similarly diagnosed AFIP cases, including those reviewed by Reese and coworkers[3,4] and by Hunter and Zimmerman.[10] No effort was made to review ex-

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haustively all other forms of congenital ocular anomalies, although some types of retinal dysplasia have been illustrated by cases bearing other primary diagnoses.

The histopathologic characteristics of the retinal alterations described by Reese and associates and by Hunter and Zimmerman were applied to the present study. These include an aberrantly organized retina with typical irregular round or oval rosettes usually formed of immature rod and cone processes, with an external limiting membrane and outer nuclear layer and occasionally a plexiform layer and inner nuclear layer in addition. In other places there may be disorganization of the normal cellular pattern, with immature cells, and often increased amounts of glial tissue. As will be apparent, an abnormal relationship of the retina to the vitreous is frequently but not invariably encountered.

## Results

### Dysplasia secondary to proliferative outgrowth of the retina

It is occasionally observed that the retina, in response to some unknown stimulus, grows out beyond the boundaries of its normal anatomic position. This situation is often encountered in the presence of other ocular anomalies such as those which accompany 13-15 trisomy. It may also be seen in instances of failure of closure of the fetal fissure with cyst formation. In some cases of bilateral or occasionally of unilateral retinal dysplasia, the major portion of the retina may be normal in structure and position, but retina will be found to have extended past the optic disk and up the persisting hyaloid stalk toward the persisting and usually hyperplastic primary vitreous (Fig. 1). In such situations, the hyperplastic retina is found to be dysplastic and may show more or less typical rosette formation, starting at the point of its departure from the subjacent pigment epithelium. In other cases, the posterior retina around the optic disk is found to be normal, but the peripheral retina, perhaps initially detached by the organizing retrolental mass, becomes hyperplastic and grows inward in a disorganized and dysplastic fashion (Fig. 2). Where there is incomplete closure of the fetal fissure, a hyperplastic retina can occasionally be found growing in ectopic locations, sometimes even outside of the globe (Fig. 3). Under these conditions, the retina is almost invariably dysplastic.

Two points are worthy of note in connection with this type of retinal dysplasia. First, it is significant that large portions of the retinas of these affected eyes (i.e., those segments lying in normal apposition to their pigment epithelium) are found to be normal. Of perhaps greater significance, however, is the observation that occasionally the proliferative outgrowth of retina may be accompanied for part of the way by an analogous proliferative outgrowth of epithelium. When

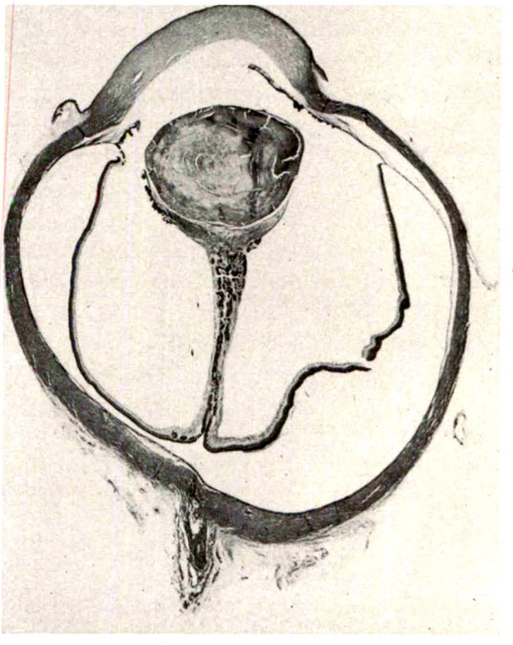


Fig. 1 (Silverstein and associates). Normal retina is present throughout most of the eye. At the optic nerve it has grown up along the persisting hyaloid stalk, and is dysplastic in this ectopic location (AFIP Case 1305972, hematoxylin and eosin, ×7).

retinal dysplasia described above, there is no evidence in these instances that the retina has ever been separated from its underlying pigment epithelium, although a small transient detachment during a critical stage of retinal maturation cannot be excluded.

There is, however, at least one form of retinal dysplasia in which it is known with certainty that the dysplastic process has occurred while the retina was in its normal position adjacent to the pigment epithelium. This form of retinopathy has been produced experimentally by infection of the fetal lamb with the attenuated bluetongue virus vaccine. This interesting biological story is described more fully in another paper.[12] Briefly, the organism employed, while modified to be nonpathogenic in the adult sheep, proves to be highly pathogenic in the young fetal lamb and produces hydranencephaly and generally a bilateral retinopathy. When the fetus is infected early in the second trimester of gestation, a progressive retinal lesion ensues, with a marked cytopathogenic effect on all cell layers of the retina. Within the first two weeks, the resulting disorganization of retinal architecture is accompanied by the formation of rosette-like structures (Fig. 9). Where destruction of the cellular elements of the retina has been extensive, the process resolves to leave an attenuated, almost acellular membrane in some areas, while in other areas a more typical picture of retinal dys-

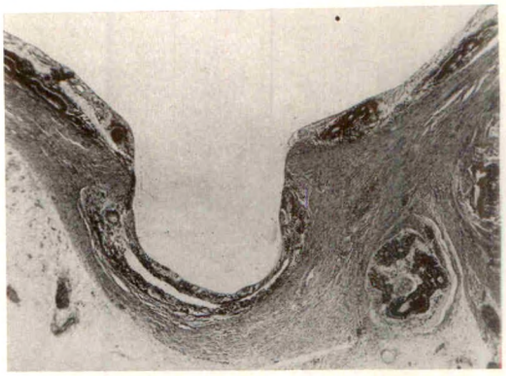


Fig. 6 (Silverstein and associates). Coloboma. Where pigment epithelium is lacking, the retina is dysplastic. Note also dysplastic retina outside the globe (AFIP Case 40932, hematoxylin and eosin, ×48).



Fig. 7 (Silverstein and associates). Cyclopia. Note the transition from normal to dysplastic retina in areas where pigment epithelium is lacking (AFIP Neg 60-4275, hematoxylin and eosin, ×5).

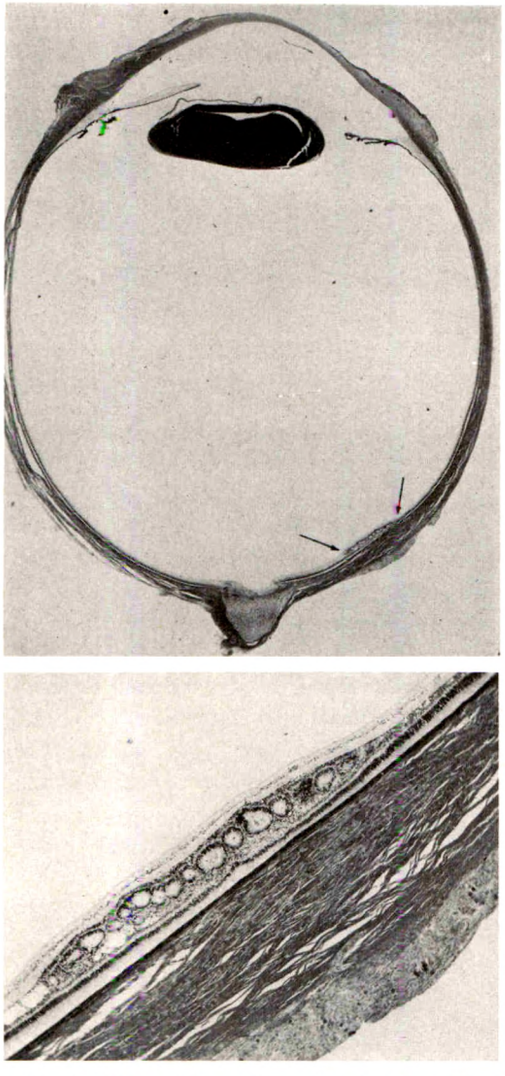


Fig. 8 (Silverstein and associates). Top: Focal retinal dysplasia (arrows) in an eye with otherwise normal retina (AFIP Neg. 64-1163, hematoxylin and eosin, ×6). Bottom: Higher power, showing rosettes which seem to reduplicate the outer nuclear layer (AFIP Neg 64-1165, hematoxylin and eosin, ×50).

plasia with rosettes and gliosis is seen (Fig. 10). It bears emphasis that at no time during the course of this retinitis can retinal detachment from the pigment epithelium be seen.

## Discussion

Retinal dysplasia appears commonly to be associated with the 13-15 trisomy syndrome, in which bilateral retinal and other ocular defects are generally associated with a variety of congenital anomalies elsewhere in the body.[3-9] It was on the basis of this concurrence of findings that Reese and coworkers[3,4] applied the term retinal dysplasia to designate the entire syndrome, at a time prior to the advent of karyologic analysis, when the genetic basis for this disease was unknown. This usage was questioned by Hunter and Zimmerman,[10] who pointed out that retinal dysplasia could be found unilaterally in a significant number of cases where other congenital anomalies were absent, and indeed in other obviously unrelated disease processes as well. These authors suggested that use of the term be restricted to the designation of a histopathologic abnormality of the retina, by virtue of the nonspecific nature of its development and the wide variety of its causes. The limited survey which we present in this paper strongly supports this view, since retinal dysplasia has been found to accompany not only 13-15 trisomy, but also congenital retinal folds,[2] sex-linked recessive Norrie's disease,[8,13-16] certain colobomas and cysts,[2,11,17] cyclopia,[18] idiopathic focal dysplasia of the retina,[10] and finally an experimental retinopathy associated with hydranencephaly produced by viral infection of the fetal lamb in utero.[12]

Those cases of retinal dysplasia which we have examined and reported herein appear to fall into four distinct categories, some of which may, however, be seen together within the same eye. Three of these categories appear to be based upon a common pathogenetic mechanism. In the first of these, dysplasia of the retina is associated with its proliferative outgrowth away from the pigment epithelium, either from the nerve head along a persisting hyaloid stalk, from the peripheral retina toward a persisting retrolental mass of hyperplastic primary vitreous, or even outside the globe in a colobomatous cyst. The second type of retinal dysplasia accompanies detachment of the developing retina from its normal apposition to the pig-

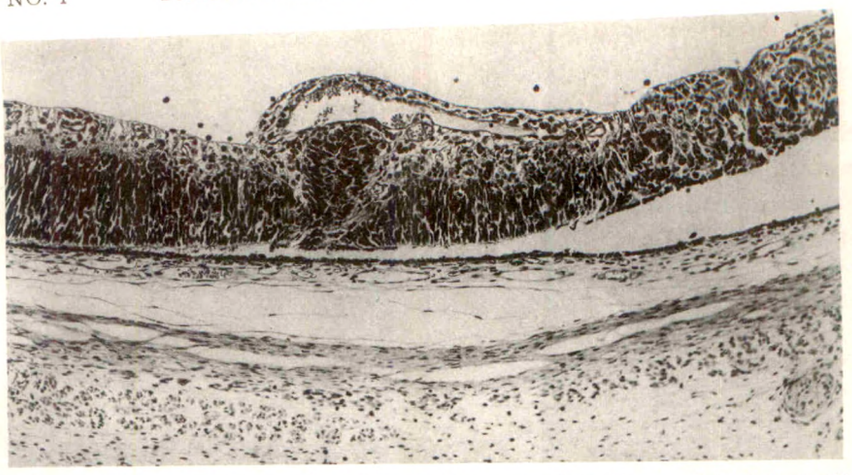


Fig. 9 (Silverstein and associates). Experimental bluetongue virus disease of fetal lamb. The animal was infected at the beginning of the second trimester of gestation and sacrificed 12 days later. Note inflammatory infiltrate, destruction of retinal cells, and immature rosette formation (hematoxylin and eosin, ×85).

ment epithelium, or perhaps may follow a failure of coaptation of the primitive layers. The third type is encountered when the retina suffers disorganized development due to a congenital absence of the pigment epithelium layer, such as may occur at the site of a coloboma. These observations appear to support the contention that the principal organizing factor in the normal histogenesis of the retina is the pigment epithelium, and that when this layer is lacking, disorganization and dysplasia may ensue. This is reinforced by the finding that even in the vitreous or behind the lens, retinal organization may be almost normal when juxtaposed to pigmented epithelium. It is of interest that the retinal pigment epithelium is also held to be responsible for the normal development of the choriocapillaris.[2]

A number of observations support the notion that it is only during a critical stage of its development that the retina is dependent upon an adjacent organizer to preserve its normal anatomic relationships. On the one hand are observations on the production of retinal hyperplasia and dysplasia with rosette formation induced by photocoagulating the retina of chick embryos,[19] following in vitro culture of retina or in vivo trephining of the eye of developing rats,[20] and x-irradiation of the human fetus in utero.[21] On the other hand, it is well known that detachment of the

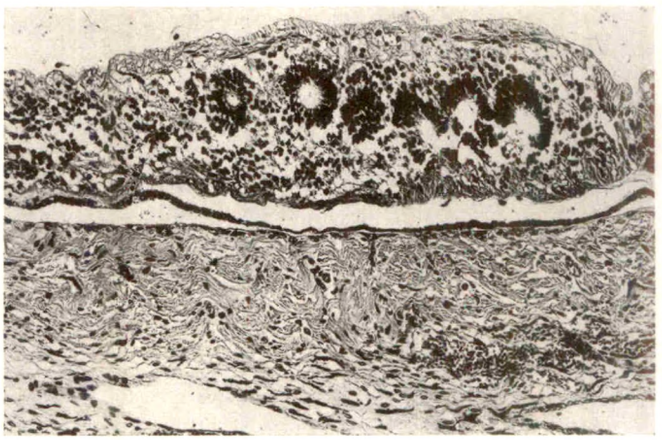


Fig. 10 (Silverstein and associates). Experimental bluetongue virus disease of the fetal lamb. At birth (105 days after infection) the inflammatory reaction has subsided, and a highly disorganized retina with gliosis and rosettes remains (Masson, ×135).

mature retina from its pigment epithelium leads to degeneration without the typical signs of dysplasia. The only instance of dysplastic changes in a mature retina which we have seen is that of a 55-year-old man described in the files of the Armed Forces Institute of Pathology (Case no. 697461), one of whose eyes showed focal retinal detachments with rosette formation. The only significant item in this patient's history was the report of a penetrating wound of the same eye some 20 years earlier. Pusey,[22] however, suggested that dysplastic rosettes might result from inflammatory processes in the adult eye.

It is obvious that retinal dysplasia is not the specific accompaniment of a single disease entity, but rather is a nonspecific response of the retina at certain stages of its development, presumably inducible by a variety of etiologic factors. Whereas the three types of retinal dysplasia described above are all associated with separation of the developing retina from its pigment epithelium, a fourth type of dysplasia appears to occur in a retina in continuous contact with pigment epithelium. Certain of these cases are characterized by a small and discrete area of dysplastic retina. While it cannot be ruled out with certainty that the developing retina had suffered a minor detachment, undergone dysplastic changes, and then reattached, no evidence survives in these cases to indicate that this indeed took place. We can be sure, however, in our studies of experimental bluetongue virus infection of the fetal lamb in utero, that the retina remained firmly attached to its pigment epithelium during the course of the disease process. It is possible, of course, that the pigment epithelium has undergone an alteration by the virus which so extensively effaced the retina, but morphologic signs of such an alteration cannot be found. It would appear rather that the extensive cytopathogenic effects of the virus and the accompanying inflammation lead directly to depopulation and disorganization of the developing retina, and that the rosettes which form represent an abortive attempt by the remaining cellular elements to effect some sort of reorganization. Once again, the change is most likely possible only at a critical stage of retinal development, since the extensive retinopathies associated with other inflammatory reactions in the more mature retina are unaccompanied by rosette formation. Although the rosette of retinoblastoma differs from that found in retinal dysplasia, it is of some interest that in this instance also the rosette represents an attempt to achieve some form of cellular organization in the less anaplastic forms of this tumor,[11] with more highly differentiated cells forming more extensive receptor processes in the form of fleurettes.[23]

The retinal dysplasia seen in this experimental model would appear to be more a component of degeneration followed by repair in the immature retina than an original dysgenesis. Whether the rosette invariably accompanies hyperplastic infolding of the retina[2,17,24] is presently unclear. Our own observations lead us to believe that rosettes may also form by the condensation of receptor cells around organizing foci of cells such as are often seen within the rosette lumen.

## Summary

Retinal dysplasia may be found in association with a variety of congenital abnormalities of the eye, some genetically transmitted and others due to exogenous influences. The dysplasias due to retinal hyperplasia, to retinal detachment or failure of coaptation, or to congenital absence of pigment epithelium suggest that orderly retinal morphogenesis may depend upon the organizing influence of an adjacent pigment epithelium. Dysplasia may also result from a necrotizing inflammatory response of the retina to infection, resulting in disorganization and abortive repair rather than true dysgenesis.

### Acknowledgment

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# AN EXPERIMENTAL, VIRUS-INDUCED RETINAL DYSPLASIA IN THE FETAL LAMB

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Influenced by the publications of Reese and coworkers,[1,2] the term retinal dysplasia has most commonly been employed in the ophthalmic literature to denote a syndrome consisting of bilateral retinopathy and a variety of other ocular and extraocular congenital anomalies. More recent advances in our understanding of genetic disease have suggested that the cases described by these authors are most probably due to a trisomy involving the 13-15 ($D_1$) group of chromosomes.[3] Hunter and Zimmerman[4] have described a series of cases of unilateral retinal dysplasia generally lacking the accompanying multiple anomalies so typical of the 13-15 trisomy syndrome, and the lesion has also been reported in the dog as a bilateral condition, again without systemic malformations.[5,6] Hunter and Zimmerman suggested that the term retinal dysplasia should thus be used to designate a histopathologic retinal lesion rather than an entire clinical syndrome. We have strongly supported this suggestion,[7] pointing out that the development of retinal dysplasia may be based upon a number of pathogenetic possibilities and probably a wide variety of etiologic agents. This paper describes the experimental production of one such type of retinal dysplasia, which follows quickly on the heels of a cytopathogenic attack upon fetal retinal cells by a viral agent.

The virus used in these studies is the bluetongue virus of sheep. Apart from the demonstration that a viral agent is capable of producing a necrotizing retinopathy with retinal dysplasia (as well as a variety of central nervous system lesions), several other fascinating points emerge from this study. First, the viral agent employed to produce the fetal disease is an attenuated, live-virus vaccine which is nonpathogenic in the adult animal. Second, the virus is only able to produce retinopathy and encephalopathy in the fetal lamb during the first half of gestation, after which the agent appears to lose its pathogenicity for the fetus, presumably in response to some maturational event in the host. Finally, whereas the wild virus appears predominantly to affect the vascular system in the adult animal and to spare the central nervous system, the principal target of the attenuated virus in the susceptible fetal host is found to be the brain, the spinal cord, and the retina. We shall describe in a later paper[8] the results of our study on the central nervous system changes accompanying this viral infection; the present paper will be devoted to a description of the ocular changes.

## MATERIALS AND METHODS

*Pregnant sheep*—The ewes employed in this study were of random mixed breed, from three to six years old. Through the courtesy of the Sheep and Fur Animal Research Branch, Animal Husbandry Research Division, Beltsville, Maryland, servicing by the ram was done under controlled conditions, and the date of conception could be established within one to two days. The gesta-

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tion period of the ovine is 150 days.

*The virus*—Bluetongue virus vaccine (Blucine) was obtained through the courtesy of Cutter Laboratories Berkeley, California. This is a vacuum-dried preparation of live virus modified by repeated serial passage through chick embryo. The vaccine was reconstituted immediately prior to use with the standard diluent provided with the vaccine, and always used on the day of reconstitution.

*Surgical procedure for intrafetal infection*—The surgical procedures employed have been described elsewhere.[9] The only technical modifications have been a discontinuance of the use of anticoagulant, and substitution of halothane-oxygen anesthesia in place of the ether-oxygen employed in earlier studies. At the desired stage of gestation, the fetus was exteriorized and injected intramuscularly in one of its extremities with 0.05 to 0.1 ml of the reconstituted bluetongue vaccine. The fetus was then returned to the uterus and a standard closure effected.

*Delivery of fetal animals and collection of specimens*—At the desired interval after intrafetal infection, the fetus (and when present, its twin, whether inoculated or not) was delivered by hysterotomy, following essentially the same procedure outlined above for the initial laparotomy. Following exposure of the fetus through the incised fetal membranes and uterus, a blood sample was withdrawn from the umbilical cord. The cord was then cut and the fetus removed for autopsy. Both eyes, the brain and spinal cord, and a representative selection of other tissues were fixed in a solution containing 20% ethanol in 10% neutral formalin for later histopathologic workup. Microscopic sections were stained with hematoxylin and eosin, and others with methyl green-pyronin.

## Results

### The normal development of the eye in the fetal lamb

In order to put into perspective some of the histopathologic changes described below, it is appropriate to review briefly some of the normal histologic stages of development of the fetal lamb's eye during the period of interest in this study, with emphasis on the development of the retina.

In many respects, after 55 days of gestation the normal eyes of fetal lambs grossly resemble those of the adult animal. Histologically, the eyes of fetal lambs taken between 55 and 86 days of gestation reveal muscular fibers external to a rudimentary fibrous sclera. The choroid appears as a delicate vascular complex in a loosely arranged stroma, with a discrete choriocapillaris already apparent in some areas. Evidence of a tenuous basement membrane similar to Bruch's membrane is seen beneath a well-ordered and continuous retinal pigment epithelium whose cells contain moderate numbers of pigment granules in the region of the ora serrata, and a decreasing degree of pigmentation as one progresses from the equator to the optic disk. Little or no pigmentation is evident in the region that will later become the tapetum lucidum. A discrete outer limiting membrane lies immediately adjacent to the pigment epithelium, with only an occasional strand of eosinophilic material visible to forecast the future rod and cone layer. At this stage the outer and inner nuclear layers are fused, and there is no evidence of an outer plexiform layer. There is a distinct inner plexiform layer, a highly cellular ganglion cell layer with but few neurons present, and a very well-vascularized nerve fiber layer covered by a fairly distinct internal limiting membrane. The most conspicuous processes in the nerve fiber layer are the vertical Müller's fibers and vessels; very few horizontal nerve fibers are observed. A primitive ciliary body and iris are present. A fine web of capillaries appears almost to surround the entire extent of the lens.

As gestation continues, the sclera and choroid become more mature and thicker. Pigmentation of the pigment epithelium becomes more pronounced and extends further backward toward the optic disk. At about 85 days of gestation, there is a beginning differ-

entiation of the cells of the still-fused inner and outer nuclear layers, with the outer nuclei becoming more elongated and the inner ones more rounded. By 96 days of gestation, the inner and outer nuclear layers are separated by a discrete outer plexiform layer. At this time also, there is an increase in the numbers of ganglion cells in the ganglion cell layer, and horizontal nerve fibers become more apparent. Whereas there is little evidence of a rod and cone layer at 90 days' gestation, some three to four weeks later this layer is present and offers a fairly mature appearance.

### Ocular pathology of lambs infected at 50 to 58 days' gestation

Twelve fetal lambs were infected with the bluetongue virus vaccine near the start of the second trimester of gestation, and they and two twins that were not injected were sacrificed at intervals thereafter. The degree of pathology in the uninjected twin was similar to that of its sibling in each instance.

*Six days postinoculation*—As soon as six days after infection of the fetus at a distant site, early changes could be seen in the retina, most prominently involving the nerve fiber layer (Fig. 1). For the most part, the lesions appeared to center on the retinal vasculature, whose endothelial nuclei were rounded and somewhat vesicular. There was a scattered perivascular accumulation of mononuclear inflammatory cells. The internal limiting membrane was irregular, and the Müller's fibers were conspicuous. Focal areas of necrosis were characterized by pyknotic and fragmented nuclei, and pink globular material appeared in place of the vertical fibers. In the nuclear layer associated with these areas, there were clear foci apparently resulting from a loss of cells. Some nuclei of glial cells in the inner plexiform layer were pyknotic. An occasional mononuclear inflammatory cell was found in the stroma of the choroid. The endothelial cells of the choroidal vessels appeared swollen.

*Nine days postinoculation*—In one animal

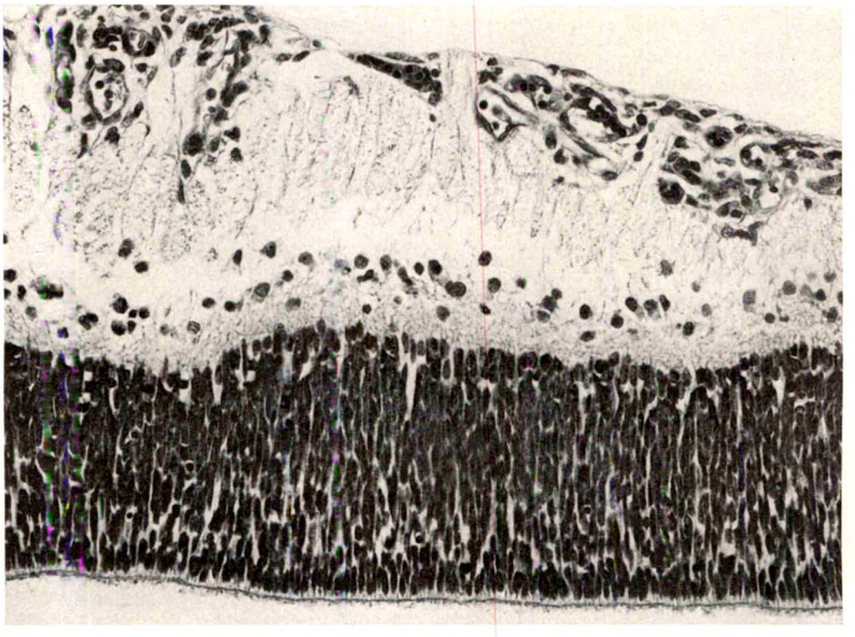


Fig. 1 (Silverstein and associates). Six days after infection of a fetal lamb at 54 days gestation, the earliest changes are centered upon the retinal vessels. Endothelial cells are rounded and prominent, and there is a scattered perivascular accumulation of mononuclear inflammatory cells. Pyknotic nuclei may be seen in the fused layers (hematoxylin and eosin, ×270).

minimal involvement of intraocular structures, consisting of a scattering of inflammatory cells in the internal layers of the retina, persisting evidence of a diffuse loss of cells in the fused inner and outer nuclear layers, and a mild diffuse choroiditis. The most conspicuous inflammatory infiltrate involved a mixed mononuclear-polymorphonuclear inflammation of the lacrimal gland and duct.

A second animal examined at this time (the twin of the one described above) was much more severely involved. The retinal changes in the eyes of this animal were analogous to those observed in the 12-day fetuses, but the degree of inflammatory infiltrate and retinal degeneration was much more extensive. There was a more widespread degeneration of the inner layers of the retina and loss of cellular elements in the nuclear layers, with monocytic infiltrates more diffuse and more prominent in the retina (Fig. 5) and choroid. There was a mild diffuse mononuclear infiltrate of the iris and ciliary body, with the retrolental vessels apparently serving as the source of a predominantly monocytic exudate. Mild, predominantly perivascular infiltrates of lymphocytes, plasma cells, and histiocytes were found in the still-fused eyelids.

*Twenty-one days postinoculation*—The inflammatory response was markedly diminished in the eyes of these animals. A few mononuclear cells persisted in the vitreous. Focal areas of necrosis involving all the areas of the retina were located in randomly scattered areas, occasionally appearing to be secondary to a severe focal choroiditis (Fig. 6). In some regions there was a persistence of folds in the retina where the nuclear layers nearly approximated the internal limiting membrane. The most prominent evidence of the earlier reaction was the presence of glial nodules in the nerve fiber and inner plexiform layers. In some areas pigment-laden cells were found in the nuclear layer, presumably a migration from the occasionally disturbed pigment epithelium layer. The lesions in the choroid were fairly well localized, and for the most part consisted of nodules of macrophages.



Fig. 4 (Silverstein and associates). Same eye as shown in Figures 2 and 3. A focal area of choroiditis is associated with a retinal fold and an increased degree of retinal necrosis (hematoxylin and eosin, ×100).

*One hundred and five days postinoculation*—In the three animals examined at this time, all signs of active inflammatory disease had disappeared. In two of the animals, the principal changes involved the retina and choroid. The atrophic retina appeared to consist of an internal and external limiting membrane enclosing in the main a glial stroma. There were a few areas where an attenuated outer nuclear layer with its rods and cones approximated the pigment epithelium, and other regions where rosettes were located, consisting of an external limiting membrane separating abortive rod and cone processes and a layer of receptor cells (Fig. 7). The pigment epithelium was incomplete in some areas and fibrous stroma and vessels from the choroid appeared to invade the retina, while glial elements from the retina appeared

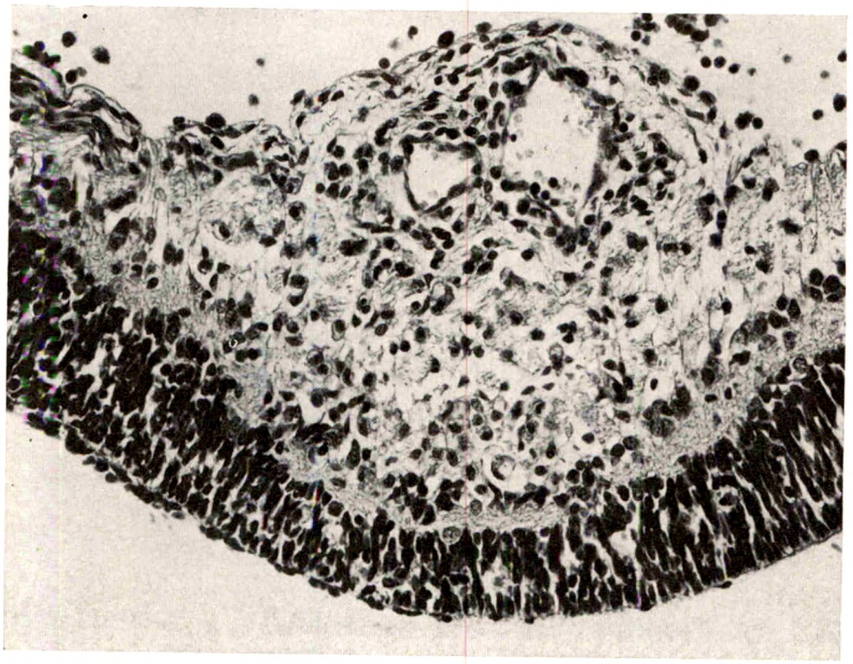


Fig. 5 (Silverstein and associates). Fifteen days after infection, there is more widespread degeneration of the inner layers of the retina in some locations, accompanied by a greater loss in the nuclear layers (hematoxylin and eosin, ×230).

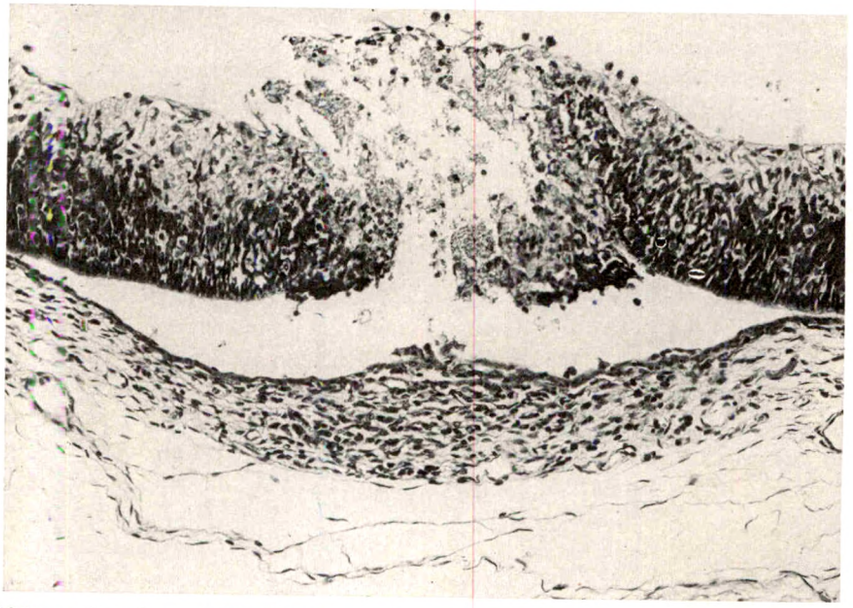


Fig. 6 (Silverstein and associates). Twenty-one days after infection, inflammatory response has markedly diminished. In this eye, less involved generally than several others, cell loss and degeneration can be seen in the nuclear layers of the retina. At the site of a focal choroiditis, the adjacent retina is completely necrotic (hematoxylin and eosin, ×140).

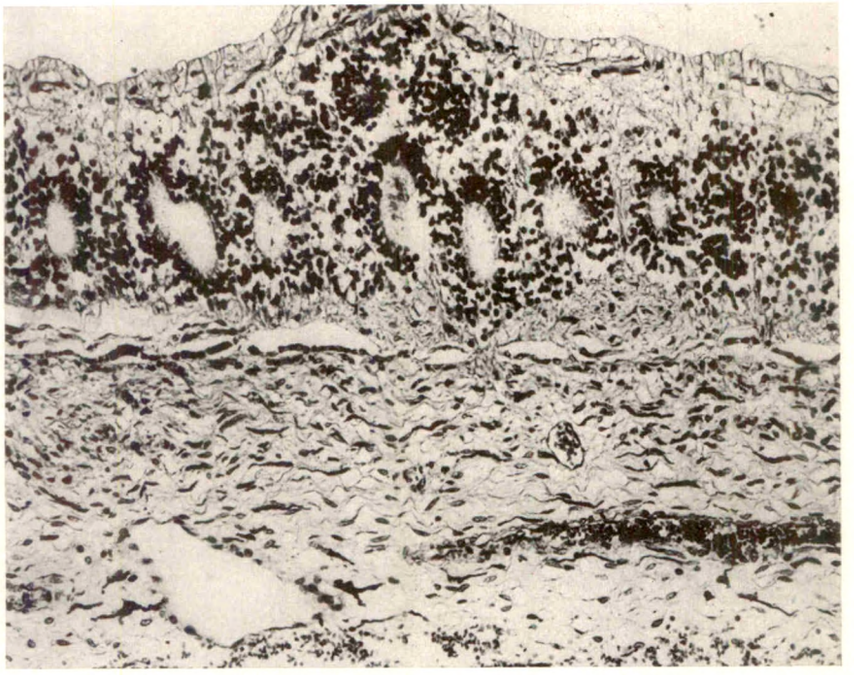


Fig. 7 (Silverstein and associates). One hundred and five days after infection, the inflammatory reaction has completely subsided. In some areas oval rosettes are present, consisting of a more or less well formed outer nuclear layer, an external limiting membrane, and abortive receptor cell processes. Note the interruptions in the pigment epithelium, through some of which fibrous tissue and vessels from the choroid appear to invade the retina, while through others glial elements from the retina penetrate to the choroid (Masson, ×140).

to invade the choroid through dehiscences in Bruch's membrane (Fig. 7). The remainder of the retina consisted of glial cells, many of which assumed a fibrillar appearance. In other areas, hyperplasia of pigment epithelium had occurred, as well as migration of these cells into the atrophic retina (Fig. 8). In yet other sites, the stroma and retina were fused, and a distinct pigment epithelium could not be observed. In some regions, the choriocapillaris was replaced by a fibrous stroma. The iris and ciliary body of these eyes appeared normal.

In one animal examined at this time, the retinal involvement was far less pronounced. There was some attenuation of the nuclear layers, and in some areas cystic changes in the nerve fiber layer. Surprisingly, the most prominent changes seen in this animal were signs of an earlier interstitial keratitis with extensive residual vascularization and scarring of the middle layers of the stroma with a degree of thinning of the central cornea.

### Ocular pathology of fetuses infected at midgestation

Six animals were infected at 70 to 75 days' gestation, and sacrificed at intervals thereafter. In contrast to the animals infected at the beginning of the second trimester of gestation, the animals infected at midgestation showed a significantly lesser degree of retinal involvement, and especially a marked diminution in the extent of mononuclear inflammatory infiltrates in the retina.

*Ten days postinoculation*—There was a moderate involvement of the vessels of the inner layers of the retina, especially at its periphery, with prominent endothelial cells and a very mild mononuclear cuffing of inflammatory cells. Occasional glial nodules were found, involving the nerve fiber layer, the in-

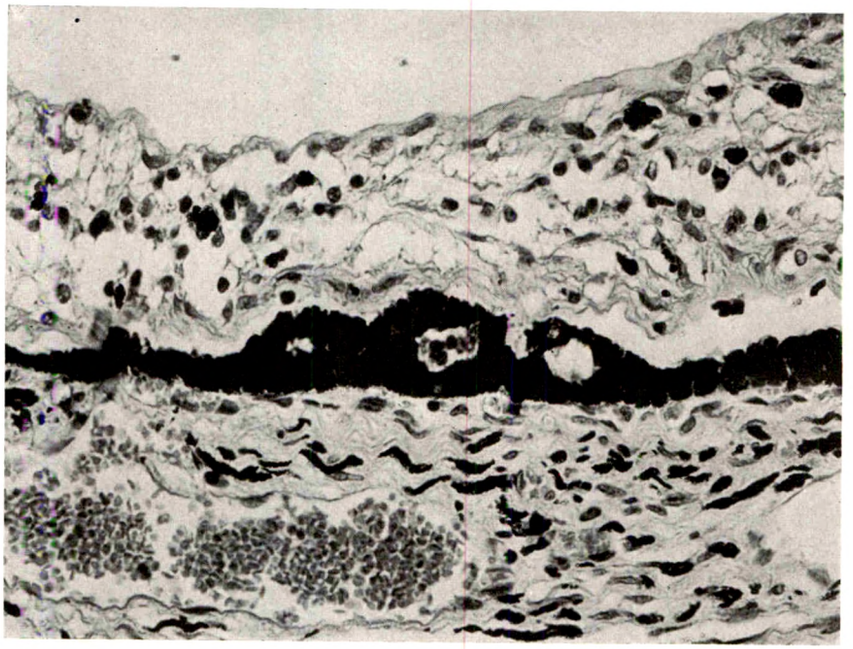


Fig. 8 (Silverstein and associates). Another area from the same eye as Figure 7. Here, destruction of the retina has been more extensive. There is hyperplasia of the pigment epithelium as well as migration of these cells into the atrophic retina (hematoxylin and eosin, ×350).

ner plexiform layer, and the inner nuclear layer. A single small focus of retinal necrosis was observed, involving all layers of the retina, apparently associated with a subjacent chorioiditis.

The most severe changes were found in the choroid. Endothelial cell nuclei were often large and vesicular, and there was a diffuse mononuclear inflammatory infiltrate extending through much of the choroid, with a scattering of neutrophils and eosinophils. A few plasma cells were present in some areas. In one eye a scattering of neutrophils was present immediately beneath the corneal epithelium. On the surface of the cornea in this area were clusters of neutrophils and necrotic debris.

*Twenty days postinoculation*—There was a persistence of the mild diffuse choroiditis at this time, involving both mononuclear and polymorphonuclear leukocytes. Throughout the retina, however, and in the almost complete absence of inflammatory cell infiltrates, there was evidence of a scattered loss of cells in the now-separated inner nuclear layer. Numerous vacuoles were seen along the entire extent of this layer, along with occasional pyknotic nuclei and nuclear fragments. Only rarely was a similar involvement of the outer nuclear layer observed. In places the inner layers of the retina appeared somewhat attenuated, and an occasional glial nodule appeared in the nerve fiber and ganglion cell layers. The rest of the eye was unremarkable.

*Sixty-three to seventy-six days postinoculation*—Only an occasional residual inflammatory cell could be found in the otherwise normal choroid at this time. The retinas also appeared fairly normal, except for areas here and there where the inner nuclear layer appeared to be somewhat thinner and less cellular than the normal control.

### Ocular pathology of fetuses infected during the last trimester

Three animals were inoculated with the live-virus vaccine at 100 to 125 days' gesta-

tion, and in general they showed little or no pathologic consequences. In one animal infected at 100 days' gestation and sacrificed three weeks later, the only lesion observed throughout the fetal eye consisted of a single glial nodule which involved the inner nuclear, inner plexiform, and nerve fiber layers. In an animal infected at 120 days' gestation and examined 10 days later, no lesions of any kind were observed. A third fetus was infected after a gestation of 125 days, with gestation then allowed to continue to normal term. This lamb was sacrificed at slightly over a month of age, or 63 days after inoculation. Only the residue of an old, apparently mild iritis was seen in one eye of this animal.

## Discussion

We have used the term retinal dysplasia in this paper to denote a certain type of histopathologic lesion, rather than a syndrome involving both ocular and extraocular pathology, in line with the suggestion of Hunter and Zimmerman.[4] It was pointed out in another paper[7] that congenital retinopathy of this type could be found not only in 13-15 trisomy, but also in Norrie's disease, in association with colobomata and cyclopia, and secondary to retinal detachment of unknown etiology. The underlying cause of these types of dysplasia appears to be the absence of the organizing function of the pigment epithelium at a critical stage of development during which it is required for orderly histogenesis. While little evidence could be adduced from the human material suggesting that inflammatory disease might also lead to retinal dysplasia, it appeared quite reasonable to assume this possibility. This might result in inflammatory detachment of the retina with consequent dysplasia, or else dysplasia in situ secondary to retinitis.

Data are presented in this paper demonstrating that a severe retinopathy with many of the features of retinal dysplasia can be produced in the fetal lamb following systemic infection by a viral agent, the bluetongue virus of the sheep. In addition to a severe encephalopathy (which will be described in detail elsewhere[8]), this virus produces in the young fetal lamb an acute retinitis characterized by a mononuclear inflammatory infiltrate and severe necrosis of the cellular elements of the developing retina. In areas where the retina is not completely obliterated, the picture of a disorganized and dysplastic retina with rosette formation is seen.

The earliest signs of retinal disease are apparent within six days after infection of the fetus, after which the disease runs a very tempestuous course and quiets down almost completely within the succeeding two weeks. At no time during the disease has the fetal retina been observed to become detached from its underlying pigment epithelium. The dysplasia encountered in this situation thus represents not a dysplastic growth of the primitive anlage deprived of the organizing influence of pigment epithelium, but an abortive effort on the part of the remaining cells of the retina to regroup and repair. While some alteration of pigment epithelial function by the virus cannot be ruled out, the absence of any morphologic signs of such a process coupled with the obvious cytopathogenic activity of the virus in the superjacent retina would seem to argue strongly against this possibility.

These data lend further support to the theory that retinal dysplasia is not a specific process, but rather an alteration which may be caused by a number of apparently unrelated mechanisms. As suggested in another paper,[7] dissociation of the immature retina from its presumed necessary juxtaposition to the pigment epithelium either by detachment, proliferative outgrowth away from the pigment epithelium, or congenital absence of pigment epithelium leads to its further abnormal (dysplastic) development. In the present situation, retinal development has progressed normally up to the point where virus-induced destruction of the various retinal elements leads to a disorganization and

attempt at repair closely resembling the dysplastic process. Of great importance to both of these mechanisms, however, is the immaturity of the retina. After a certain stage of development, the retina is presumably too highly differentiated to be able to support typical dysplastic changes. It is probably for this reason that we do not see dysplasia of the more mature retina following detachment or necrosis secondary to retinitis or chorioretinitis.

Several other points deserve more than passing mention in connection with the present studies. The first concerns the critical nature of host factors in determining the pathogenicity and virulence of a given organism. More and more we are becoming aware that the use of attenuated live-virus vaccines, although rendered nonpathogenic for the adult, may not always be used with impunity in a pregnant recipient, by virtue of some special susceptibility of the immature fetus. Indeed, the first hint that this was the case with the bluetongue vaccine was provided by observations in the field,[10] and later experimentally,[11,12] of so-called "dummy" (hydranencephalic) lambs born to ewes that had been immunized with the vaccine during pregnancy. This danger presupposes, of course, that the agent in question is able to cross the placenta, a condition which may not obtain in all instances. The bluetongue viral vaccine obviously does cross the placenta, as is witnessed by fetal infection when either the mother or, in several instances in this study, a twin is inoculated.

It is of further interest that the altered status of the host may affect profoundly the nature of the disease process produced by a given pathogen. In the adult sheep, the wild strain of the bluetongue virus produces a pathology centered on vascular changes with accompanying subcutaneous and fascial edema, erosion and ulceration of oral mucous membranes, and necrosis of skeletal and cardiac muscle.[13] There is no evidence that the adult suffers any central nervous system or ocular pathology during the course of its disease. When the egg-passed attenuated virus is introduced to the fetus either by maternal immunization or directly, as in the present study, a completely different disease is produced in the fetal host. This consists, early in gestation, of massive necrosis of neural and retinal tissues, resulting in hydranencephaly and retinal degeneration and dysplasia with few if any of the hallmarks of the natural adult disease.

Finally, the changing nature of the fetal disease with increasing age of the fetal host presents a most fascinating biological problem. Infection of the fetus at the beginning of the second trimester of gestation (50-58 days) is almost invariably accompanied by massive destruction of neural and retinal cells. The inflammatory infiltrates which accompany this disease are predominantly monocytic and histiocytic, with few lymphocytes and even fewer plasma cells in evidence. At about midgestation (75-100 days), the nature of the disease changes markedly. Now there is little evidence of cytopathogenicity and necrosis in either the brain or the retina, but instead only widely scattered glial nodules in the retina and a change of venue of the inflammatory reaction to the choroid. The inflammatory infiltrate at this stage is more highly lymphocytic, with plasma cells now in evidence. By 100 to 125 days gestation, infection of the fetus fails to produce any retinal pathology at all, and those mild inflammatory infiltrates formed elsewhere possess large numbers of both lymphocytes and plasma cells.

There exist at least two reasonable although not mutually exclusive explanations for the changing nature of this fetal disease and the difference between fetal and adult susceptibility to this attenuated live virus. It is possible that the immature neural and retinal cells of the developing fetus are peculiarly susceptible to the cytopathogenic effects of this viral agent. With increasing maturation, it might be supposed that some biochemical or physiologic change in these cells renders them impervious or otherwise

unsusceptible to viral attack. On the other hand, there is some indirect evidence to suggest that the maturational event which protects the older fetus and adult from the more destructive disease may be immunologic in nature.[12,14] It is known that the mammalian fetus may develop immunologic competence to a given antigen at a very distinct time in its development.[15] If the fetal lamb were to achieve immunologic competence to the bluetongue virus at about midgestation then it would be able to participate in its own defense against the viral infection, sufficiently perhaps to prevent infection and destruction of neural and retinal cells. This possibility finds some support in the changing cytologic picture of this disease as described above, and in some preliminary evidence which we have obtained that neutralizing antibody to the bluetongue virus can be found in the infected fetus only after some 75-100 days' gestation.

Finally, the interrelationship of retinopathy with hydranencephaly such as is described in this paper draws our attention to possible retinal involvement in other forms of encephalopathy. Urman and Grace[16] have published a pathologic description of a congenital, autosomal recessive encephalomyopathy of calves. In addition to a primary disturbance in myogenesis and internal hydrocephalus, an invariable finding was complete retinal detachment with dysplastic retinal tissue in the stalk connecting the optic disk to the posterior surface of the lens. Hydranencephaly with congenital blindness has also been reported in calves,[17] but here the blindness is apparently cortical, since the eyes were reported to be ophthalmoscopically and microscopically normal. Hill and coworkers reviewed the ocular signs associated with human hydranencephaly.[18] Although a variety of ocular signs have been noted in association with hydranencephaly, the single case on which they present histopathologic findings shows extensive retinal degeneration and gliosis, although without typical dysplasia. These authors emphasize the multiplicity of pathogenetic mechanisms that may lead to hydranencephaly, a point which we have emphasized in our discussion of retinal dysplasia.

## Summary

Retinal dysplasia, accompanying extensive destructive retinopathy and hydranencephaly, has been produced in the fetal lamb with the attenuated bluetongue virus, a live-virus vaccine nonpathogenic in adult sheep. With increasing maturity, the nature of the ocular disease changes in the fetus, until late in gestation it demonstrates a typical adult resistance to the viral agent. Some of the host factors which may modulate the apparent pathogenicity of infectious agents have been discussed, along with some of the maturational events which may account for the increased resistance of the older fetus and adult to this viral agent.

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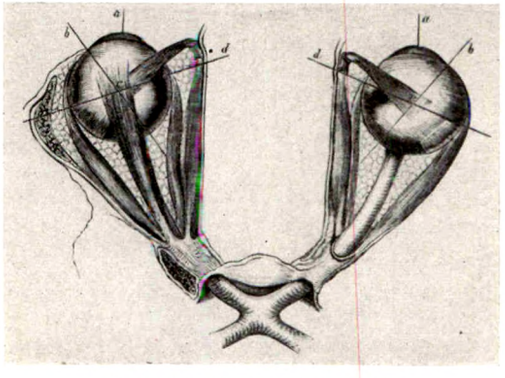
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OPHTHALMIC MINIATURE

Diagram illustrating the axes of revolution on which the eyeball is moved by its different muscles. Lawrence, W.: A Treatise on the Diseases of the Eye (Hayes, Isaac, ed.). Philadelphia, Lea and Blanchard, 1847.

# ANTERIOR SEGMENT ISCHEMIA FOLLOWING SCLERAL BUCKLING IN SICKLE CELL HEMOGLOBINOPATHY

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The "anterior segment ischemia syndrome" comprises a set of severe complications of retinal detachment surgery. This syndrome may frequently nullify an otherwise successful scleral buckling procedure,[1-4] due to the development of postoperative keratopathy, intraocular inflammation, hypotony, and cataract. Its pathogenesis has been attributed to several different factors at the time of surgery, including (1) interruption of the anterior ciliary arteries,[5,6] (2) damage to the long posterior ciliary arteries,[1,7] and (3) placement of an encircling element.[5]

Although generally an uncommon complication of scleral buckling operations, we have observed anterior segment ischemia, in a very high percentage of patients with sickle cell-hemoglobin C disease (SC disease) who have undergone retinal detachment surgery. The following nine case reports illustrate this complication of scleral buckling in SC disease. Possibilities for prophylaxis and therapy are presented, based on hypotheses regarding the pathogenesis of anterior segment ischemia in eyes with a propensity for intravascular sickling.

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## MATERIALS AND METHODS

The hospital records of all hemoglobinopathy patients undergoing ocular therapy during the last five years (August, 1964, to September, 1969) were reviewed. Six patients from the Wilmer Institute Residents' Service were found to have had scleral buckling operations. One patient (Case 1) had bilateral retinal detachment procedures. The hemoglobinopathy of all six cases was found to be the SC type by hemoglobin electrophoresis. All patients had been personally examined by at least one of us by indirect ophthalmoscopy and biomicroscopy. During the same time interval, in which over 100 patients with various types of hemoglobinopathies (SS, SA, SC, SThal, SD, AC, CC) were actively studied for retinal abnormalities, no other hemoglobinopathy patient was found to have retinal detachment. An additional SC patient (Case 5), who had retinal detachment surgery prior to the five-year review period, is also included in this report. The pertinent clinical and surgical details of these seven cases (eight eyes) constitute part of the material of this report (Fig. 1). Cases 8 and 9, from the University of Illinois Eye




Fig. 1 (Ryan and Goldberg). Key to illustrations of Cases 1 through 7 (Figs. 2 through 9).

TABLE 1

RESULTS OF SCLERAL BUCKLING PROCEDURES IN SICKLE CELL HEMOGLOBIN C RETINOPATHY*

| | Case 1 | | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
|---|---|---|---|---|---|---|---|---|
| | OS | OD | | | | | | |
| Hemoglobin electrophoresis | SC | SC† | SC | SC | SC | SC | SC | SC |
| Age, sex, race | 26 M/N | | 15 F/N | 22 F/N | 34 F/N | 19 M/N | 38 M/N | 32 M/N |
| HCT (in %) at surgery | 42 | 38 | 31 | 33 | 37 | 47 | 40 | 34 |
| Date of scleral buckling | 7/1/69 | 9/26/69 | 8/14/64 | 6/25/65 | 8/3/65 | 1/6/61 | 11/24/64 | 11/29/68 |
| Anesthesia (general or local) | General | Local | General‡ | Local | Local | General | General | General‡ |
| Rectus muscles detached | 0 | 0 | 1 | 0 | 1 | 2 | 1 | 0 |
| Encircling band | Yes | Yes | Yes | No | No | Yes | Yes | Yes, "tight" |
| Diathermy or cryothermy | Cryothermy | Cryothermy | Diathermy | Diathermy | Diathermy | Diathermy | Diathermy | Diathermy and cryothermy |
| Long posterior ciliary treated | Yes | No | Probably | Yes | No | Probably | No | Possibly |
| Scleral dissection or exoplant | Exoplant | Exoplant | Scleral dissection | Scleral dissection | Scleral dissection | Scleral dissection | Scleral dissection | Exoplant |
| IOP (Schiøtz in mm Hg) after surgery | 17 | 28 | Normal | Sixth post-operative day: 15 | 16 | 12 | Soft, intra vitreal injection | 6 |
| Preoperative vision | 20/30 | 20/200 | 20/400 | 20/25-1 | 20/70-1 | 20/40 | CF | 2/200 |
| Postoperative vision | 20/25 | HM | 20/30 | 20/20-1 | 20/20 | HM | LP | NLP |
| Length of follow-up | 7 months | 4 months | 5 years | 5 months | 4 years | 5 months | 4 months | 13 months |
| Postoperative ischemia syndrome | Yes | Yes | No | No§ | Yes | Yes | Yes | Yes |

* With the exception of Case 1, cases are listed in the order of increasing severity of the anterior segment ischemia.
† Preoperative transfusion, RE. Hb S 40%, Hb C 40%, Hb A 20%.
‡ In Case 2, blood pressure fell from 115/65 to 90/65 mm Hg during operation; in Case 7, blood pressure fell from 110/70 to 90/60 mm Hg during operation.
§ Retinal ischemia present anterior to diathermy.

and Ear Infirmary, presented with retinal detachments after analysis of the results in Cases 1-7. They were operated upon using the prophylactic recommendations cited below, and are also included. To our knowledge, there have been no other SC cases that have had retinal detachment surgery in our hospitals.

Cases 2-7 are listed in increasing order of severity of the anterior segment ischemia (Table 1). Cases 8 and 9 did not develop ischemia (Table 2).

In order to compare the incidence of postoperative anterior segment ischemia in SC patients with that in patients with normal hemoglobin, a review was made of the first 20 consecutive retinal detachment cases on the Wilmer Residents' Service from each of the last five years.

## Case report

*Case* 1—This 26-year-old man had chronic reduction of vision in his right eye, and complained of loss of his superior field in his left eye.

*Left eye:* The extent of the retinal detachment and distribution of sea-fans[8] are shown in Figure 2. On July 1, 1969 a scleral buckling procedure was performed on the left eye (Fig. 2). Table 1 lists the technical factors that might have predisposed the patient to develop the anterior segment ischemia which occurred postoperatively (Fig. 2-bottom). The intense inflammatory response failed to respond to a multitude of therapeutic measures but subsided gradually over approximately three weeks. Vision returned to 20/25. Midstromal iris atrophy and a few scattered posterior subcapsular opacities in the lens were the only residua.

*Right eye:* His right eye had a virtually complete retinal detachment and extensive vitreous traction (Fig. 3). Preoperatively, the patient underwent partial exchange blood transfusion in addition to other prophylactic maneuvers (which are recommended below). The buckling procedure is described in Figure 3 and in Table 1. Due to laboratory error, the patient did not achieve the recommended[9] 60% hemoglobin A prior to surgery. Postoperatively, he developed anterior segment ischemia again. Low molecular weight dextran (Rheomacrodex), topical corticosteroids, and atropine were of no avail, as the eye went on to phthisis (Fig. 3).

*Case* 2—This 15-year-old girl developed a rhegmatogenous retinal detachment six weeks following heavy photocoagulation to sea-fan neovascularization in the temporal periphery of her right eye (Fig. 4). A scleral buckling operation was done under general anesthesia, during which mild systemic hypotension occurred (Fig. 4-bottom right). The lateral rectus muscle was temporarily detached; the area overlying the temporal long posterior ciliary nerve and artery was treated with scleral diathermy, and an encircling band was placed. Despite these events, the postoperative reaction was limited to modest swelling and tenderness of the conjunctiva and eyelids, and no definite signs of anterior segment ischemia were noted. The retina was re-attached. Five years later, vision was 20/30.

*Case* 3—This 22-year-old woman gave a presumptive history of recurrent vitreous hemorrhage in the right eye, and was found to have a retinal hole and localized retinal detachment at 9 o'clock (Fig. 5). A small scleral diathermy procedure was carried out over this area, and involved the temporal long posterior ciliary complex (Fig. 5-bottom). No muscle was removed at the time of operation, which was done under local anesthesia, and no encircling band was placed. The postoperative course was uneventful, except for ischemia of the retina anterior to the treated area. The retina was re-attached. Vision was 20/20-1.

*Case* 4—This 34-year-old woman had recurrent vitreous hemorrhages in both eyes. The patient underwent a limited trap-door procedure in the left eye under local anesthesia for a retinal hole which was under traction (Fig. 6). The lateral rectus muscle was temporarily removed during the procedure, but the long posterior ciliary nerve and vessel complex was spared. No encircling strap was placed (Fig. 6-bottom). Postoperatively, there was anterior chamber haze with keratic precipitates as well

TABLE 2

Results of scleral buckling using prophylactic measures (including effective partial exchange blood transfusion) vs. sickling

| | Case 8 | Case 9 |
|---|---|---|
| Hemoglobin electrophoresis | SC | SC |
| Age, sex, race | 37 M/N | 37 M/N |
| HCT at surgery % | 37 | 47 |
| Date of buckling | 6/25/70 | 7/17/70 |
| Anesthesia | Local | Local |
| Rectus detached | 0 | 0 |
| Encircling band | Yes | Yes |
| Diathermy or cryothermy | Cryothermy | Cryothermy |
| Long posterior ciliary treated | No | No |
| Scleral dissection or exoplant | Exoplant | Scleral dissection |
| IOP (Schiøtz) at end of surgery | Slightly elevated | 29 mm Hg |
| Preoperative vision | CF | LP |
| Postoperative vision | 20/400 | HM |
| Follow-up | 10 months | 6 weeks |
| Postoperative ischemia syndrome | No | No |

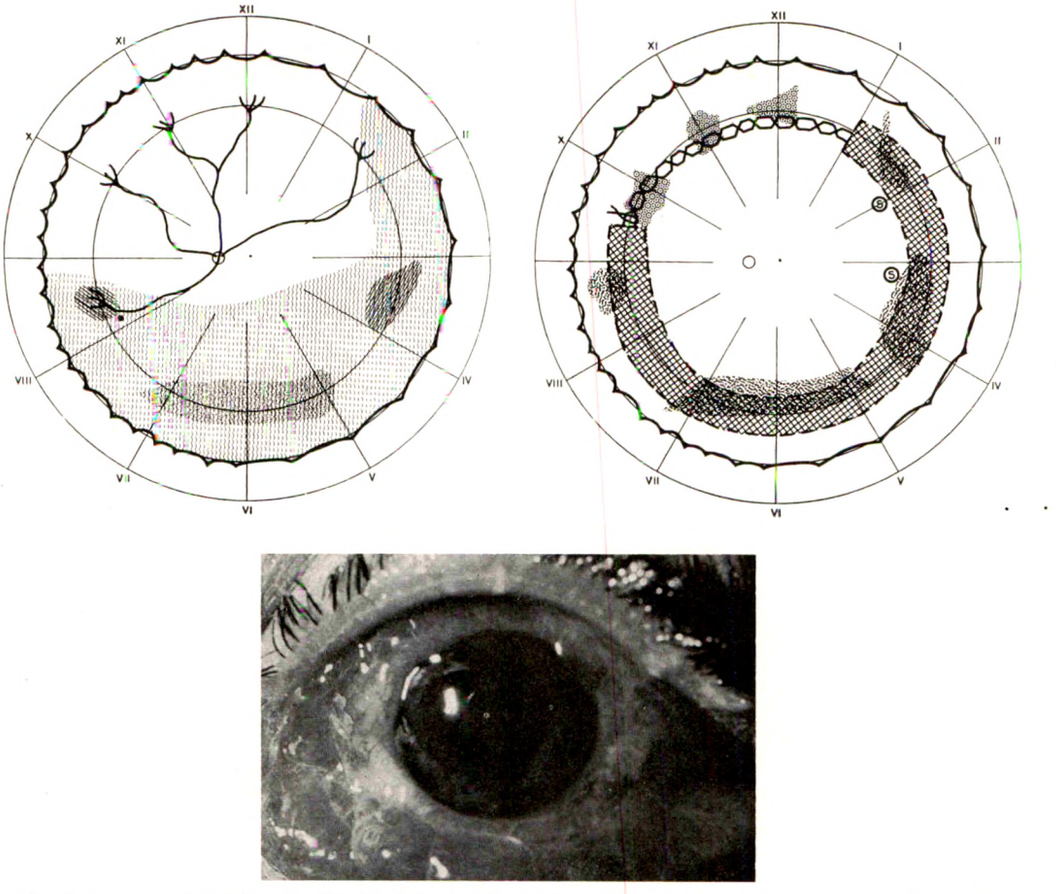



Fig. 2 (Ryan and Goldberg). Case 1, left eye. Top left: The retinal detachment in the left eye from 1:15 to 8:45 o'clock spares the macula. Sea-fans are present at 8:30, 10, 11, 12, 1:30 o'clock. Old white and fresh blood are present inferiorly, and glial proliferation is seen at 3:30 and 8:30 o'clock. At operation, holes were found at 3:30 o'clock, anterior and posterior to the glial scar. Top right: The operation is diagrammed. Sea-fans at 10, 11 and 12 o'clock were photocoagulated. Cryothermy (freeze and refreeze) was applied to sea-fans at 8:30 and 1:30 o'clock, to the glial scar at 3:30, where two holes were discovered, and to the region of the old hemorrhage from 5 to 7 o'clock. A No. 20 silicone strip was placed as an exoplant from 1:00 to 9:30 o'clock, and a No. 40 encircling band was placed around the globe, and clipped at 9:30 o'clock. Sclerotomies were performed at 2:00 and 3:15 o'clock with release of moderately xanthochromic fluid. This eye did well following resolution of anterior segment ischemia, and vision is 20/25. Bottom: The same eye is shown six days after scleral buckling. Anterior segment ischemia is manifested by chemosis and irregular necrosis of the iris (with production of an irregular pupil).

as vitreous haze. Since endophthalmitis was considered possible, and because systemic antibiotics were already being routinely administered, systemic steroids were added to the postoperative therapeutic regimen. Four years later, the retina was attached, and vision was 20/20.

*Case* 5—In 1961, this 19-year-old man underwent a scleral buckling operation with diathermy for a retinal detachment in his right eye (Fig. 7). The medial and inferior rectus muscles were temporarily detached. Postoperatively, there was corneal edema, aqueous ray and hypotony. Endophthalmitis was suggested, and a course of systemic penicillin, streptomycin, chloromycetin, and corticosteroids was begun.

One month later there were posterior synechiae, irregular dilatation of the pupil, moderate aqueous ray, cortical cataracts, and innumerable cells and dense haze in the vitreous. The retina was completely attached.

Five months later, when last seen, vision in the right eye was hand movements only. Only a red fundus reflex could be discerned, due to residual blood from several episodes of recurrent vitreous

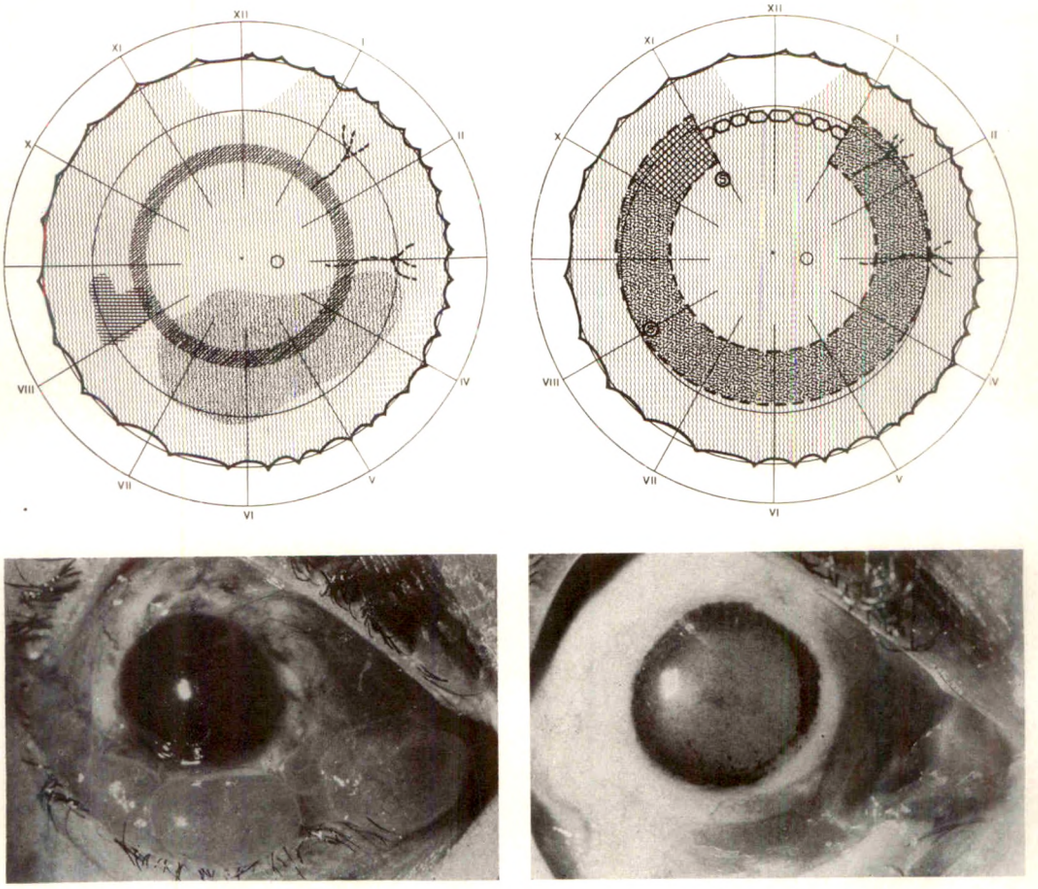



Fig. 3 (Ryan and Goldberg). Case 1, right eye. Top left: Only a small area of retina (from 11:30 to 12:30 o'clock) was attached in the right eye of Case 1. Marked vitreous traction, with an equatorial, circumferential band of condensed vitreous (resembling a purse string) was seen. Retinoschisis was present at 8:30 o'clock adjacent to a small hole, which was visualized only at operation. Obliterated old sea-fans were seen at 1:30 and 3 o'clock, and old vitreous blood obscured the fundus from 3:15 to 7:30 o'clock. Top right: The operative result is illustrated. Meridional rows of cryothermy were applied from 1 to 10 o'clock. A No. 281 silicone tire exoplant was secured from 1 to 11 o'clock with an encircling No. 240 band. A sclerotomy at 8 o'clock yielded large amounts of fluid, but no further fluid could be obtained from a sclerotomy at 11 o'clock. The retina never settled. Severe anterior ischemia developed, and the eye progressed to phthisis. Bottom left: The right eye of Case 1 is shown 14 days after scleral buckling. The cornea is clear, as it is in the later Figure to the right, but marked chemosis and irregular pupillary dilatation were present. Bottom right: The same eye is shown 11 weeks after scleral buckling. Phthisis bulbi, with cataract and extensive iris necrosis, has occurred.

hemorrhage. The intraocular pressure was 7 mm Hg. The prognosis for useful vision appeared hopeless.

*Case* 6—This 38-year-old man developed a total retinal detachment in his right eye (Fig. 8). At surgery, a normal blood pressure was maintained under general anesthesia. The patient underwent a scleral buckling procedure with diathermy, a buried implant, and an encircling band (Fig. 8-bottom). The long posterior ciliary neurovascular complexes were spared, but the inferior rectus muscle was temporarily detached. Postoperatively, conjunctival hyperemia, chemosis, shallow anterior chamber with choroidal effusion, keratic precipitates, fibrin clot and cataract developed. Thirteen days postoperatively, the patient was started on systemic corticosteroids. The eye had progressed to the prephthisical stage when last examined four months postoperatively.

*Case* 7—This 28-year-old man had a scleral buckling procedure under general anesthesia for a total retinal detachment in the right eye (Fig. 9).

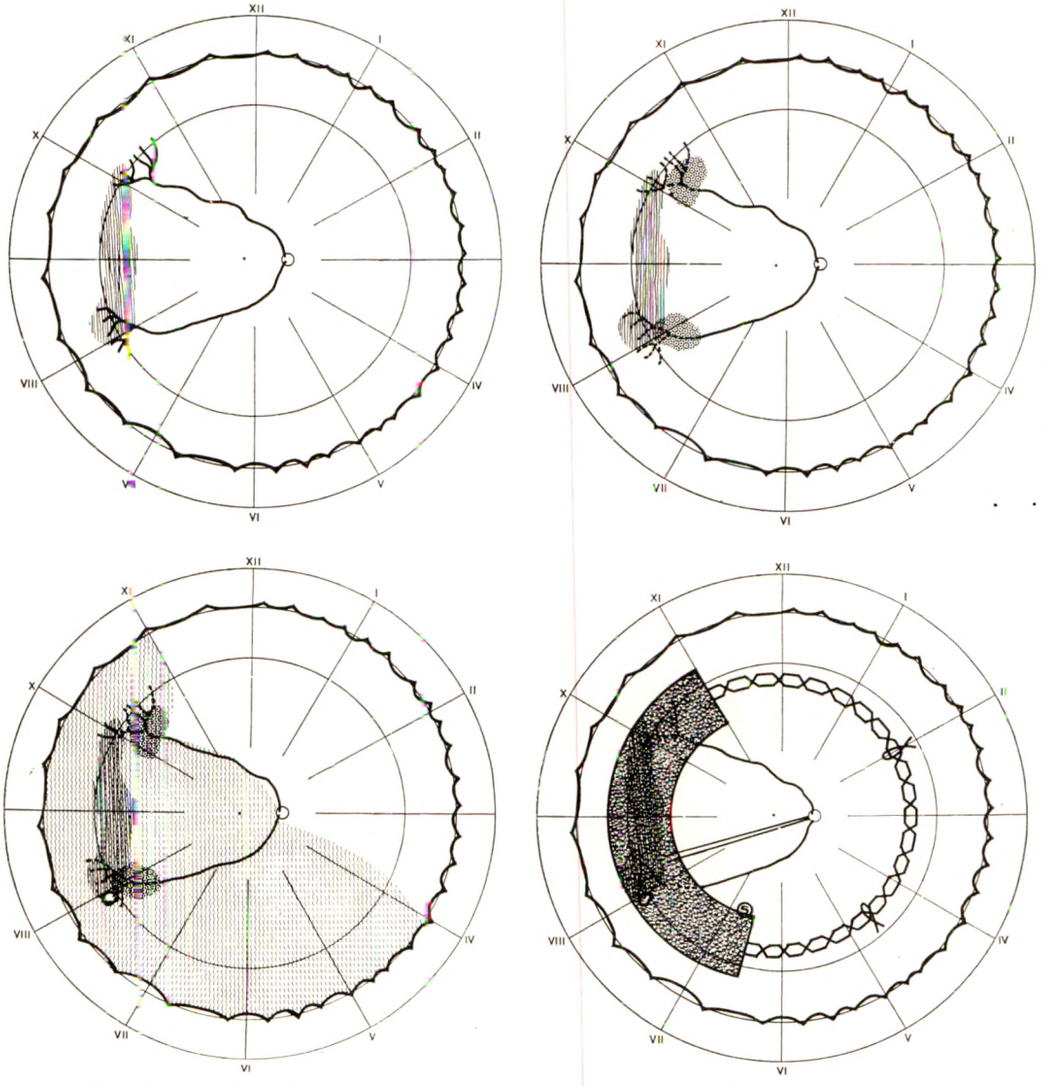


Fig. 4 (Ryan and Goldberg). Case 2. Top left: On initial examination, this patient had arborizing sea-fans at 8 and 10 o'clock, with glial membrane or vitreous sheet connecting the two areas of neovascularization. Top right: Photocoagulation (Zeiss) with overload No. 1 intensity and the 3° image field produced avascularity of the fans. Bottom left: Forty-four days after photocoagulation, retinal detachment with a hole at 8 o'clock was noted. Bottom right: The operation is illustrated. Diathermy was placed at the retinal hole at 8 o'clock and in the bed of a lamellar scleral dissection from 6:30 to 11 o'clock. An 8 mm wide silicone strip was implanted, and a No. 40 encircling band was clipped at 2 o'clock. The vitreous sheet remained over the buckle from 7:30 to 9:30 o'clock. A white retinal traction fold ran from the buckle at 8:30 to the disk, causing macular distortion and vision of 20/30. There was no anterior segment ischemia.

Blood pressure fell from 110/70 to 90/60 during surgery. Diathermy and cryothermy were applied to the retinal breaks. Silicone sponge exoplants were applied meridionally, and an encircling band was pulled tightly following subretinal fluid drainage (Fig. 9-center). No muscles were detached. Postoperatively, he developed chemosis, cloudy cornea, pigmented keratic precipitates, shallow anterior chamber, rapidly intumescent cataract, and yellow vitreous haze which prevented fundus examination. Because of a presumptive diagnosis of endophthalmitis, systemic therapy with penicillin, chloromycetin, and corticosteroid was instituted. Eight months later, the eye was phthisical, and had iris

necrosis, cataract, hypotony, and no light perception (Fig. 9/bottom). The eye was obtained at autopsy and demonstrated histopathologic signs of anterior segment ischemia.

*Case* 8—This 37-year-old man with SC hemoglobin, had a total, bullous retinal detachment of the left eye (Fig. 10). Partial exchange transfusion raised his hemoglobin A to 64%. A four and one-half hour exoplant and cryothermy procedure was carried out under local anesthesia. A stellate gan-

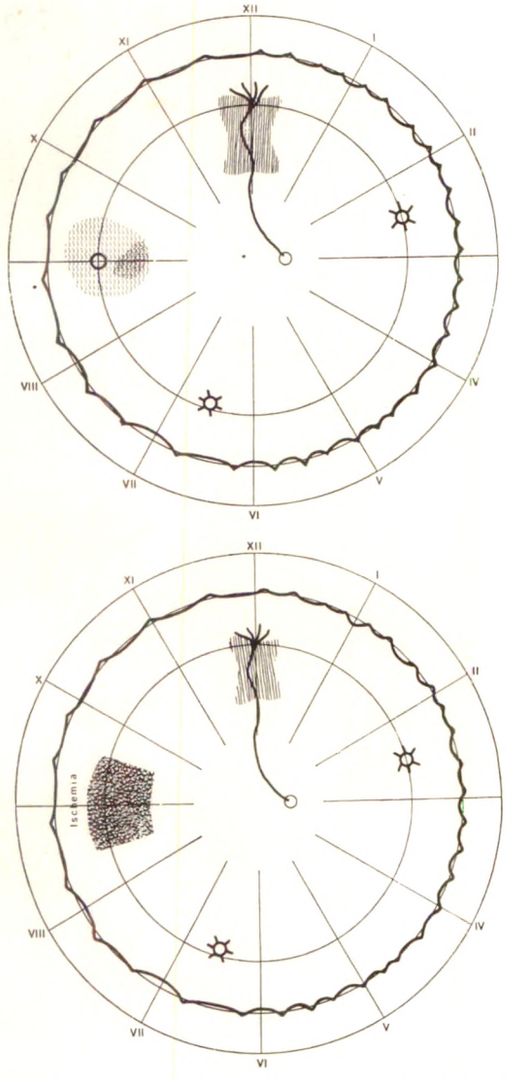



Fig. 5 (Ryan and Goldberg). Case 3. Top: The retinal hole, and localized retinal detachment and vitreous blood are seen at 9 o'clock in the right eye. A seafan is present at 12 o'clock, and two black sunbursts[8] are at 2:30 and 6:30 o'clock. Bottom: The operation was a trap door procedure with diathermy, but no implant was used. Ischemia developed in the retina anterior to the area of treatment, but central vision remained normal.

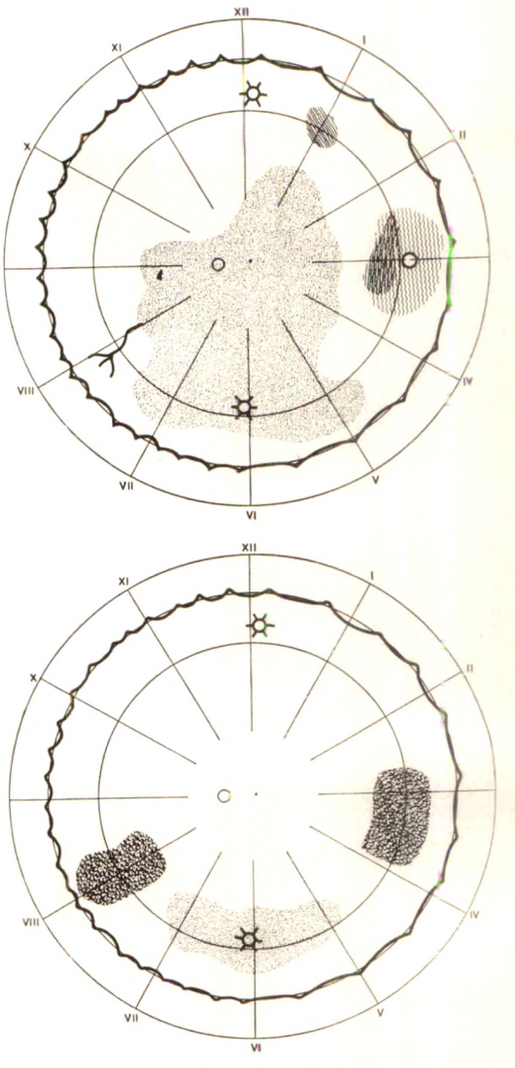



Fig. 6 (Ryan and Goldberg). Case 4. Top: A hemorrhage obscuring the posterior pole is shown. Black sunbursts are present at 12 and 6 o'clock. Glial retinal scars extending into the vitreous can be seen at 1 and 3 o'clock. A retinal hole with localized retinal elevation is present at 3 o'clock. A single sea-fan at 7:45 o'clock is also seen. Bottom: The operation is illustrated. Diathermy was placed at the 3 o'clock hole and at the 7:45 sea-fan. A temporal scleral trap door procedure was carried out, with diathermy placed in the bed of the trap door and with implantation of a sheet of silicone sponge. Minimal anterior segment ischemia resulted. Subsequently, vision was 20/20.

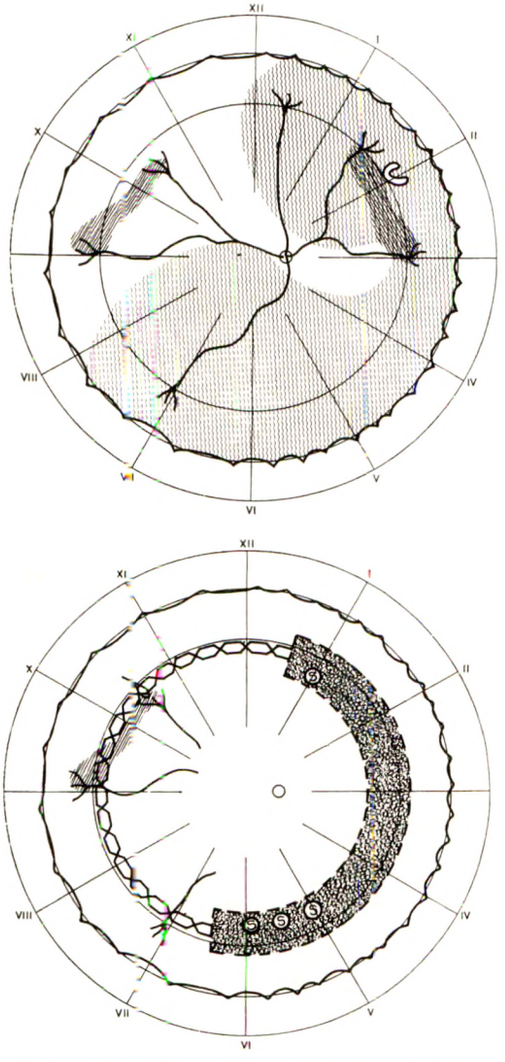


Fig. 7 (Ryan and Goldberg). Case 5. Top: A horseshoe tear at 2 o'clock and the retinal detachment are seen. Sea-fans are present at 12:30, 1:30, 3, 7, 9 and 10:30 o'clock, along with glial sheets at 2 and 9:30 o'clock. Bottom: At operation, a lamellar scleral bed was cut from 12:30 to 6:30 o'clock. Diathermy was placed in the bed, and an encircling polyethylene tube was tied at 10:30 o'clock. Sclerotomies were performed at 1, 5, 5:30, and 6 o'clock. Postoperatively the patient developed anterior segment ischemia, the visual results of which negated the successful reattachment of his retina.

glion block, retrobulbar priscoline, intravenous papaverine, and continuous nasal oxygen (which was maintained during the operation and for the next two days) were administered. There were no sympathomimetics used for pupillary dilatation or retrobulbar anesthesia. One horseshoe tear at 1:30 o'clock was found adjacent to a sea-fan,[8] and was frozen. Two No. 279 silicone tires were sutured to

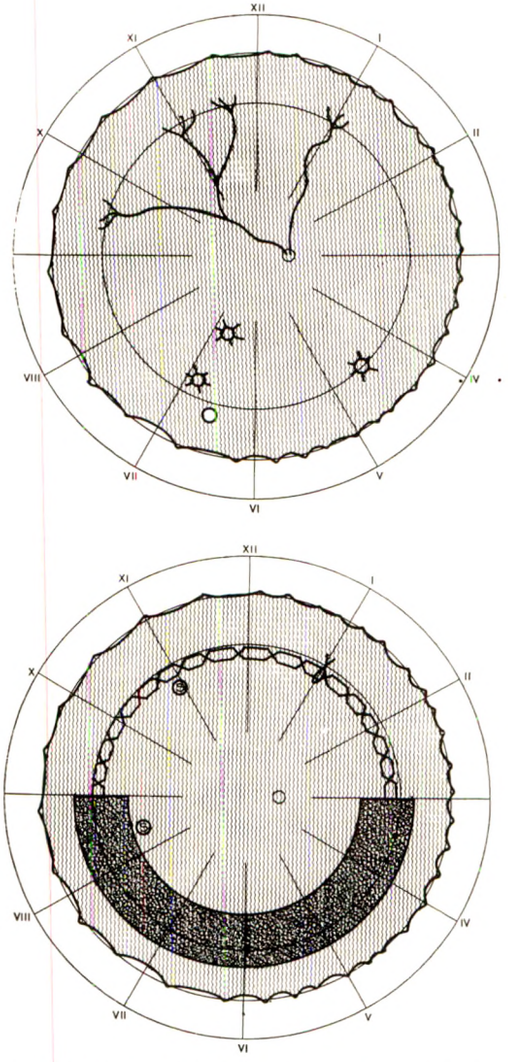
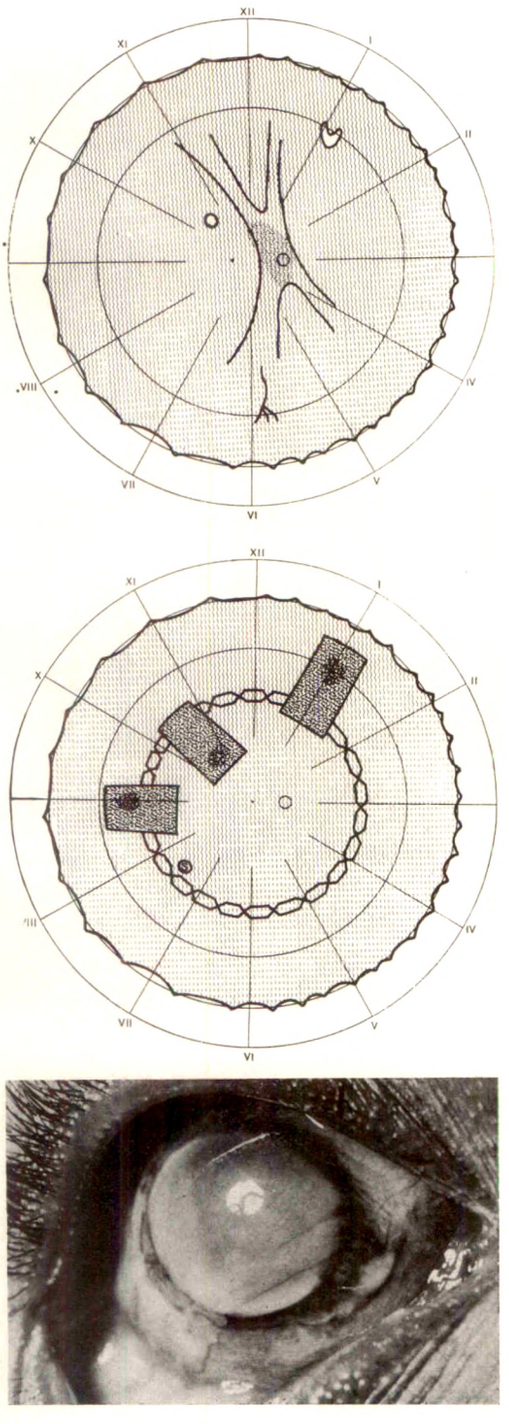


Fig. 8 (Ryan and Goldberg). Case 6. Top: A total retinal detachment and a hole at 6:30 o'clock are seen. Black sunburst scars are present at 4:30 and 6:45 o'clock. Numerous obliterated and patent areas of neovascularization are seen at 9:30, 11, 11:30, and 1 o'clock. Bottom: The operative procedure is shown. The inferior rectus was detached. A lamellar scleral bed was dissected from 3 to 9 o'clock and diathermy was placed in the bed. A No. 31 silicone implant was left in the bed, and a No. 40 encircling band was tied at 1 o'clock. Two sclerotomies were performed (at 8:30 and 11 o'clock). Postoperatively, the retina remained detached, and the patient developed severe anterior segment ischemia.

the sclera (Fig. 10-bottom), and subretinal fluid was drained. Intraocular pressure was slightly elevated at the end of the operation. Anterior segment ischemia did not occur. Ten months postoperatively, the retina was completely attached. Vision had improved from counting fingers at three feet to 20/400.

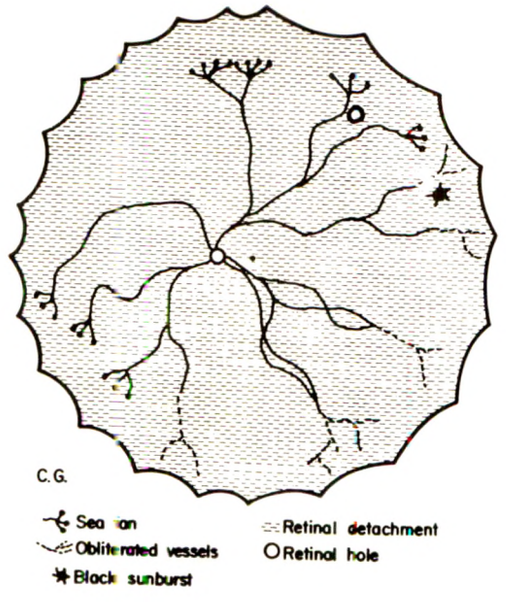
*Case* 9—This 37-year-old man had a total retinal detachment in the left eye. A dense vitreous traction band pulled on the retina above and below the macula (Fig. 11). Partial exchange transfusion raised his hemoglobin A to 67%. A four and one-half hour scleral buckling procedure was performed under local anesthesia. A stellate ganglion block, retrobulbar priscoline, intravenous papaverine, and continuous nasal oxygen (which was maintained during the operation and for the next two days) were administered. No sympathomimetics were used for pupillary dilatation or for retrobulbar anesthesia. One large tear adjacent to the 3 o'clock sea-fan was found, and was frozen. A 15 mm wide scleral undermining (Fig. 11-bottom) was dissected from 11 to 8 o'clock (clockwise), and cryothermy placed in its bed. The long posterior ciliaries were spared. A 13 mm wide implant was buried beneath the scleral flaps after subretinal fluid was drained. An encircling band raised the intraocular pressure slightly at the end of surgery. Muscles were not detached. Despite the extensive scleral dissection, anterior segment ischemia did not occur. Six weeks postoperatively, the retina was flat at the buckling site, but was elevated posterior to the implant due to extensive vitreous contraction.

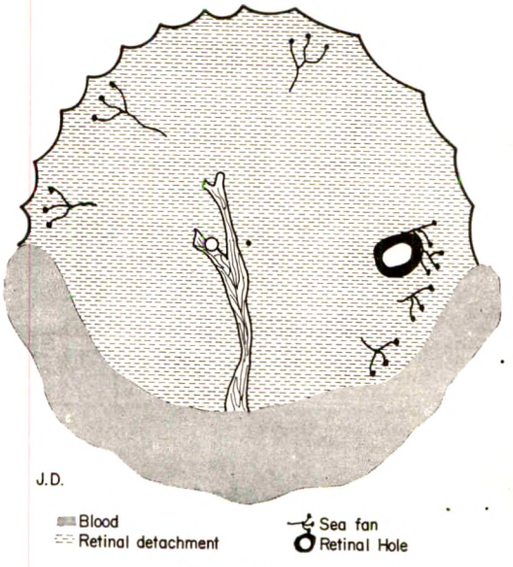



## Comment

*Proliferative sickle retinopathy*—Fluorescein fundus angiography in SC cases has demonstrated an area of total retinal avascularity immediately peripheral to the characteristic neovascular proliferations (sea-fans),[8,10-13] where an occlusive process appears to involve retinal capillaries and small

Fig. 9 (Ryan and Goldberg). Case 7. Top: The total retinal detachment, dense vitreous bands, old vitreous blood, large retinal tears at 11 and 1 o'clock, and neovascularization at 5:45 o'clock are illustrated. Center: At operation, the retinal holes, plus an additional hole at 9 o'clock, were treated with a central spot of diathermy and encircling cryothermy. A 5 mm silastic sponge was placed under the 11 o'clock hole, and 3 mm sponges were placed under the 9 and 1 o'clock holes. A No. 240 band encircled the eye posterior to the equator. A sclerotomy was performed at 7:30 o'clock posterior to the band. The patient developed severe anterior segment ischemia, which progressed to phthisis. Bottom: The same eye as photographed eight and one-half months after scleral buckling. There is phthisis bulbi with cataract and extensive iris necrosis.



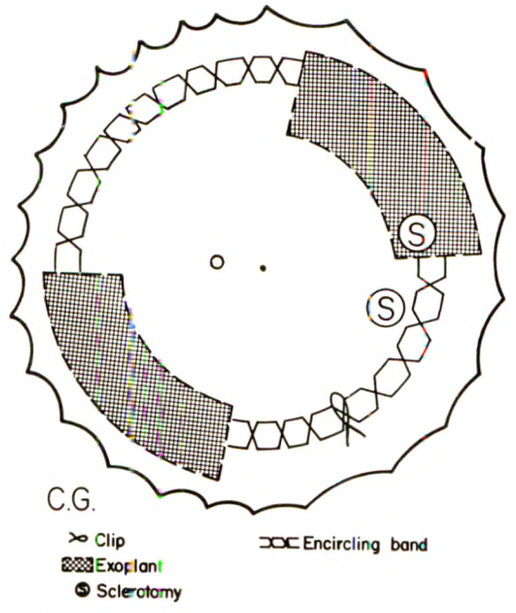




Fig. 10 (Ryan and Goldberg). Case 8. Top: The left eye of Case 8 had a total detachment with a single supero emporal retinal hole adjacent to a sea-fan. Bottom: Anterior segment ischemia did not develop postoperatively, despite two large buckles, prolonged operating time, elevated intraocular pressure and an encircling band. Several prophylactic measures, including partial-exchange blood transfusion, had been taken preoperatively.

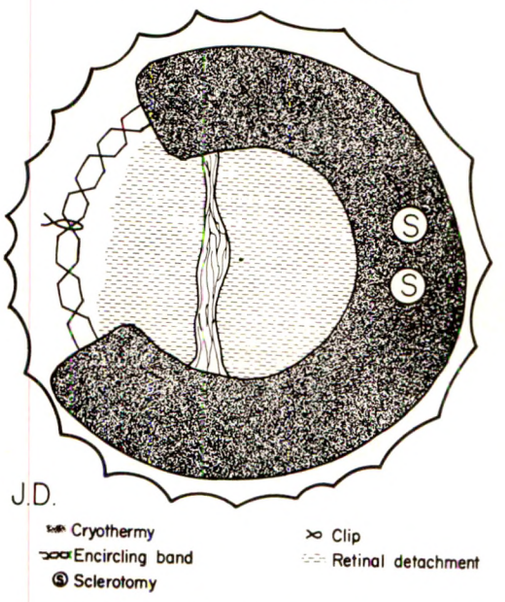



Fig. 11 (Ryan and Goldberg). Case 9. Top: The left eye of Case 9 showed extensive vitreous contraction and hemorrhage. A single retinal hole was found adjacent to a sea-fan at 3 o'clock. Bottom: A 15 mm wide scleral dissection was created for a 13 mm wide silicone implant from 11 to 8 o'clock. Despite prolonged operating time, elevated intraocular pressure, an encircling band and very extensive surgery, anterior segment ischemia did not occur. Several prophylactic measures, including partial-exchange blood transfusion, had been employed preoperatively. The retina reattached at the buckling site, but remained elevated posterior to the implant because of extensive vitreous membrane formation and contraction.

arterioles. Evidence suggests, therefore, that such eyes are ischemic even prior to therapeutic intervention.[11-13] Ischemia, itself, may contribute to the development of retinal detachment, even in individuals with normal hemoglobin.[14]

Over the last six years 45 SC patients have been studied by one of us at the Wilmer Institute and at the University of Illinois Eye and Ear Infirmary, during which eight patients developed or presented with retinal detachment. It is apparent that retinal detachment is a significant complication of SC disease (but seemingly not in other types of hemoglobinopathy), even allowing for bias of ascertainment of cases. A previous histologic report[15] confirms the severity of retinal pathology in SC disease.

An effort was made to determine the approximate frequency of SC hemoglobin in one of our hospital's Negro population with retinal detachment. Sixty-one Negroes had had retinal detachment surgery at the Wilmer Institute during the last five years. Therefore, our six SC patients originating from this hospital comprise approximately 10% of the Negro retinal detachment cases during this interval. The 10% frequency may actually be an underestimation, since hemoglobin electrophoresis was not performed on all Negro retinal detachment patients. The association of SC hemoglobin with retinal detachment is emphasized by the realization that it represents an approximately 33-fold increase over the frequency of SC hemoglobin in the general Negro population (which is about 0.3%).[16]

One of the alleged reasons that Negroes have less retinal detachments than Caucasians is their diminished frequency of vitreous degeneration.[17-19] Conversely, the high frequency in Negro retinal detachments of SC retinopathy is apparently related to the extensive vitreous degeneration, contractions, and hemorrhage which are seen in this disorder.[8,11,12]

In an attempt to compare the frequency and severity of anterior segment ischemia following scleral buckling in SC patients with similar parameters in the nonsickling population, the first 20 consecutive retinal detachment cases performed on the Wilmer Residents' Service for each of the last five years were reviewed. Of these 100 cases, 68 were Caucasians and 32 were Negroes without systemic or ocular evidence of sickle cell disease. There were three instances (one Negro) of anterior segment ischemia in these 100 cases (3%), as opposed to five of seven eyes in the SC cases (71%) during the same interval. Of the nonsickling cases, one was particularly severe, and developed phthisis bulbi. In the SC cases, two eyes were prephthisical and two were phthisical at the last follow-up examination.

*Anterior segment ischemia*—Six of the 10 eyes reported here showed some ischemic signs. The anterior segment ischemia syndrome consists of necrotic changes in the cornea, iris, ciliary body, lens and anterior chamber, presumably secondary to ischemia and hypoxia. Striate keratopathy, with folds in Descemet's membrane and corneal edema, is frequently the first and most prominent sign. Progressive conjunctival edema may then become apparent. Iris necrosis is often manifested by irregular dilatation of the pupil and shrinkage towards the area of greatest necrosis. Cataract formation may begin first on the side of greatest hypoxia, as indicated by the iris necrosis, and is usually complete in severe cases within three months. Hypotony is often marked. The anterior chamber may become shallow, possibly in association with ciliary body and choroidal detachment.

Haziness of the ocular media in this syndrome may mimic the appearance of postoperative, infectious endophthalmitis, and, when coupled with chemosis and keratopathy, may erroneously suggest a diagnosis of infectious panophthalmitis. It is instructive that in at least three of these patients (Cases 4, 5, and 7) an infectious etiology was considered seriously enough to warrant intensive therapy with systemic antibiotics.

The pathogenesis of anterior segment ischemia has been related to interruption of the anterior ciliary arteries (those major arteries, usually seven in number, coursing through the rectus muscles),[5] to occlusion of one or both of the long posterior ciliary arteries,[1,2] as well as to the constricting effect of an encircling band.[1-3,5] Various experimental methods have been employed[6,7] in an attempt to reproduce this syndrome. However, the exact pathogenesis is unknown, and any or all of the above factors may play responsible roles. It would seem, however, that this disorder is related to impaired circulation and hypoxia of the anterior segment. Similar clinical findings have been noted in patients who undergo no surgery, but who have ischemia on the basis of atherosclerosis or other disease processes affecting the vascular supply of the eye.[20]

*Surgical factors*—No positive, consistent correlation (Table 1) can be made in this series of patients between the development of ischemia and any one of the following technical aspects of the surgery: (1) Detachment of the rectus muscle. Two patients (Case 1, both eyes, and Case 7) developed anterior segment ischemia even though no rectus muscle was detached. (2) Use of an encircling band. Case 4 did not have an encircling element, and developed ischemia, whereas Case 2 had a band but did not become ischemic. (3) Treatment over the long posterior ciliaries. In Cases 1 (right eye), 4, and 6, these vessels were spared, but ischemia occurred, whereas the long posterior ciliary artery was diathermized in Case 2, but ischemia did not occur. (4) Cryothermy vs diathermy. Cases 1 and 7 were treated with cryothermy, whereas diathermy was used in Cases 4, 5, and 6, but all developed ischemia. (5) Exoplant vs implant. Cases 1 and 7 had exoplants without scleral surgery, but were ischemic nonetheless. (6) Ocular hypertension. No case had a significant elevation of tension. (7) Systemic hypotension. Normal blood pressure in Cases 1, 4, 5, and 6 did not prevent ischemia. The possibility that the extent of the retinal detachment and vitreous traction (and thus the extent of the required surgery) can be correlated with the development of anterior segment ischemia must be considered, since several eyes with the most difficult detachments developed the most severe ischemia. However, Case 2 had diathermy $> 120°$) and did not develop ischemia, whereas Case 4 had 60 degrees of diathermy and did develop ischemia. Case 2 did not develop anterior segment ischemia, despite the following technical maneuvers which might theoretically predispose to ischemia: systemic hypotension during anesthesia, scleral surgery and diathermy with involvement of the long posterior ciliary complex, detachment of a rectus muscle and placement of an encircling band. Also, Cases 8 and 9, with severe detachments and extensive surgery, did not develop ischemia (Table 2). Thus, it appears that no common surgical denominator can be derived from the technical aspects of scleral buckling in these cases which can be held responsible for postoperative anterior segment ischemia.

*Nonsurgical factors*—Certain nonsurgical factors can be correlated with lack of development or less severity of anterior segment ischemia following retinal detachment operations in SC patients. For example, Cases 2-4 are females (Table 1), and were affected either mildly or not at all. Cases 2 and 3 were also characterized by having a lower average age and a lower average hematocrit than those patients who did develop anterior segment ischemia (Table 3). Since vascular occlusions occur intermittently and progressively during the lifetime of SC patients, it is possible that enough patent vasculature existed in the younger patients to allow adequate perfusion of the anterior segment during and following surgery. However, even the factor of youthfulness in Case 5 did not prevent the development of anterior segment ischemia (which may have been related in his case to temporary detachment of two rectus muscles).

It appears possible that SC hemoglobin

TABLE 3

SCLERAL BUCKLING IN HEMOGLOBIN SC DISEASE
(Cases 1–7, eight eyes)

| | Age (avg. years) | Hct (avg. %) | Sex | | Anesthesia | | Rectus Off | Encirc. Band | Dia-thermy | Cryo-thermy | Im-plant | Exo-plant | Postoperative Vision | | Rx for Endoph-thalmitis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | M | F | Loc. | Gen. | | | | | | | 20/30 | HM | |
| No ischemia (2 eyes) | 19 | 32 | 0 | 2 | 1 | 1 | 1 | 1 | 2 | 0 | 2 | 0 | 2 | 0 | 1 |
| Ischemia (6 eyes) | 29 | 39 | 5 | 1 | 2 | 4 | 3 | 5 | 4 | 3 | 3 | 3 | 2 | 4 | 3 |

plays a responsible role in the development of anterior segment ischemia. The clinical severity of the different sickle hemoglobinopathies is directly related to the rate of increase of viscosity of blood during deoxygenation.[9] The concentration of hemoglobin S and the degree of interaction between the various hemoglobins are the major determinants of this rate. The viscosity of blood containing sickled erythrocytes is proportional to the product of the percentage of sickle hemoglobin and the square of the hematocrit value.[9] A higher hematocrit with a concomitant, increased viscosity predisposes to the multiple thrombotic events characteristic of this disease. These considerations may be helpful in explaining the frequent occurrence of vascular occlusive manifestations in patients with certain heterozygous sickling disorders, such as SC, who do not have appreciable anemia.[9,21,22] The lower hematocrit in Cases 2 and 3 may have allowed less viscosity, better perfusion, and, therefore, improved oxygenation of the anterior segment as compared with those cases with higher hematocrits.

The phenomenon of intraoperative, intravascular sickling is well recognized, and is thought to be related to relative hypoxia in association with anesthesia.[23-28] While most sicklers are subject to this hazard, SC patients with their nearly normal hematocrits (frequently 35 to 40%) seem particularly prone to intravascular sickling under these conditions.

An instructive, though distressing, operation was that for the right eye of Case 1. This was the first instance, to our knowledge, in which the association between anterior segment ischemia and SC hemoglobin was known preoperatively. Thus, a large number of prophylactic measures (listed in Table 4) were utilized in the management of this eye. Despite all these measures, anterior segment ischemia developed postoperatively. Extensive cryothermy and a large exoplant, which were necessitated by the marked vitreous traction, may have contributed. However, similar surgery in Case 9 did not cause the ischemic syndrome. A laboratory error in Case 1, however, led to inadequate exchange transfusion preoperatively, such that only 20% of the patient's hemoglobin was normal hemoglobin A at the time of surgery. This is markedly less than the 60% hemoglobin A which is the recommended minimal preoperative goal of partial exchange transfusion in sickle cell disease. If nothing else, Case 1 underscores the association of postoperative anterior segment ischemia with SC disease, since a conscious and reasonable effort was taken to avoid or minimize most, if not all, of the other factors that might ordinarily predispose to ischemia.

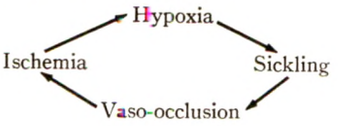
Cases 8 and 9 represent, perhaps the strongest argument for the role of intravascular sickling in the development of anterior segment ischemia following scleral buckling. In these two patients extensive and prolonged operations were performed after exchange transfusion had provided greater than 60% hemoglobin A. Anterior segment ischemia did not develop in either case.

*Recommendations*—The data of Charache

TABLE 4

POSTOPERATIVE ANTERIOR SEGMENT ISCHEMIA IN SICKLE RETINOPATHY

Postulated pathogenesis:




Recommended prophylaxis:

Preoperative:
1. Local anesthesia without sympathomimetics
2. Stellate ganglion block, papaverine administration
3. Pupillary dilatation with parasympatholytics only
4. Partial exchange transfusion
5. Lowered intraocular pressure

Intraoperative:
1. Supplemental oxygen
2. Minimization of peritomy
3. Avoidance of rectus muscle detachment or traction
4. Avoidance of long posterior ciliary vessels
5. Diathermy vs cryothermy (?)
6. Exoplant vs scleral implant (?)
7. Subretinal drainage
8. Avoidance of encircling band if possible (one is frequently necessary because of extensive vitreous traction)

Recommended postoperative therapy:
1. Supplemental oxygen
2. Pupillary dilatation
3. Papaverine (?)
4. Low molecular weight dextran (?)
5. Adrenal corticosteroids (?)
6. Anticoagulants (?)

and Conley[9] support the concept that all the clinical manifestations of sickle cell disease are attributable to the consequences of intravascular sickling of erythrocytes. Because of the lack of any other consistent surgical factor in these patients which could be correlated with anterior segment ischemia (Table 1), it would appear that the sickling process is probably also related in some causal way to the development of anterior segment ischemia in our patients. That this may be so is underscored by the high percentage of sicklers who developed this disorder following scleral buckling in comparison with the nonsickling population. Also, as noted above, those patients previously transfused successfully tolerated the scleral buckling procedure well. Consequently, the recommendations in Table 4 for clinical management of SC patients who require retinal detachment surgery are based on attempts to avoid intraoperative and postoperative ischemia, hypoxia, and sickling. The onset of sickling in the eye, as elsewhere, sets up a vicious cycle of events leading to decreased perfusion, with further ischemia, hypoxia, and sickling (Table 4).

Since the effects of anterior segment ischemia are sometimes irreversible, prophylaxis is preferable to therapy. The common objective underlying these recommendations (Table 4) is increased perfusion and oxygenation, with decreased sickling and ischemia.

Because of the danger of sickling during parturition, pregnant women with SC disease have been effectively managed prior to delivery by partial exchange transfusion.[27] This exchange of normal red blood cells for those containing SC hemoglobin has also been recommended prior to general surgical

procedures.[26,28] Complications from parturition and surgery can usually be minimized if partial exchange transfusion results in a red blood cell mass in which about 60% of erythrocytes have normal hemoglobin A. It would seem reasonable, therefore, to treat scleral buckling cases similarly. Since even local anesthesia obviously does not eliminate all causes of ocular ischemia and hypoxia that occur during retinal detachment surgery, this recommendation applies even when retrobulbar anesthesia is employed. The possibility, however, of inducing serum hepatitis or septicemia by partial exchange transfusion must be considered.

Cryothermy with an exoplant would theoretically appear to be more advantageous than diathermy and a scleral disection. In any event, drainage of subretinal fluid will soften the eye and tend to counteract any tendency towards decreased vascular perfusion.

Other prophylactic and therapeutic measures with potential merit are listed in Table 4.[29-38]

## Summary

Ten eyes of nine sickle cell-hemoglobin C patients (SC) underwent retinal detachment surgery. Six eyes showed signs of anterior segment ischemia postoperatively, and one showed signs of retinal ischemia. Four eyes became phthisical or prephthisical. In three cases, anterior segment ischemia was erroneously thought to be infectious endophthalmitis.

In a sampled hospital population, 71% of buckled eyes of SC patients developed anterior segment ischemia, whereas only 3% of nonsickling eyes developed this postoperative complication during the same five-year period. Patients with SC hemoglobin thus appear particularly vulnerable to anterior segment ischemia following scleral buckling.

Lower hematocrit, younger age, and female sex were associated with clinically less severe postoperative findings.

Technical surgical factors did not seem to influence the presence or absence of postoperative anterior segment ischemia. Partial exchange blood transfusion and additional measures were employed in three cases. When the patients' hemoglobin A was increased to more than 60%, anterior segment ischemia did not develop despite extensive, prolonged scleral buckling operations.

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# SURGICAL CATGUT FOR SEGMENTAL BUCKLE IN RETINAL DETACHMENT

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The introduction of the segmental scleral buckling procedure by Custodis[1,2] in 1951 revolutionized important concepts in retinal detachment surgery. The essential factor of this technique was that the sclerochoroidal buckle pushed the diathermized choroid into apposition with the retinal breaks during the actual operation. Presently, the aseptic and polymorphous silicone rubber has replaced most other implants. Experimental[3] and clinical observations showed that the sclerochoroidal buckle gradually flattened following the operation, but this had no adverse effect on a reattached retina. This observation and concern over the reported complications, mainly pressure necroses and infections,[4-7] prompted the introduction of absorbable scleral implants.

Chromic surgical gut was the first to be used,[8] followed by fascia lata,[9] and others.[10-17] Absorbable implants did not become popular, mainly because of their questionable sterility and the difficulty in obtaining most of them.

Experimental work[18] showed that thick chromicized surgical gut which was completely buried within a scleral fold created a scleral buckle which persisted for at least two months. Histologically, a mild transient inflammatory reaction of the uvea was noticed along the buried gut and this was considered an advantageous side effect for the reattachment of the retina. The duration of the buckle was thought to be adequate for use in idiopathic retinal detachments. The purpose of this paper is to report a suitable technique.

The present results were obtained in 21 successive operations. The detachments covered up to one-half of the retinal surface, had one or more breaks within the detached area, and included aphakic eyes and cases with detached maculas. Cases with fibrous vitreous bands, massive vitreous retraction, giant tears, and total detachments were not operated on with this method.

## DESCRIPTION OF OPERATION

General anesthesia was preferred but in about half of the operations local anesthesia with 2% xylocaine HCl with the addition of adrenalin 1:1000 was used satisfactorily.

After lateral canthotomy, the presenting rectus was detached, the sclera exposed, and traction sutures were placed under the adjacent recti in order to rotate the eye to the desired position. The retinal break was localized by transillumination and the first orientating diathermic coagulation applied with a blunt 1 mm diameter electrode (Storz E-5212). Additional ophthalmoscopically visible coagulations with a 0.5 mm long non-perforating diathermy needle with insulated base (Storz E-5262) were placed to surround the break. Instead of diathermy, cryo-applications were used in about half the cases for the additional treatment of the choroid.

Two millimeters behind the orientating coagulation a single-incision scleral groove was formed parallel to the limbus and involving one-third to one-half the circumference of the globe. The groove was formed by incising the external one-half of the scleral layers with a No. 15 Bard-Parker blade and then pushing the wound edges of the incision anteriorly and posteriorly with the blade until the base of the groove was 3 to 4 mm wide (Fig. 1). Occasionally, sharp undermining of the posterior scleral edge was necessary, especially when the groove was located behind the equator. For this a No. 66 angled Beaver blade proved safe in avoiding sceral

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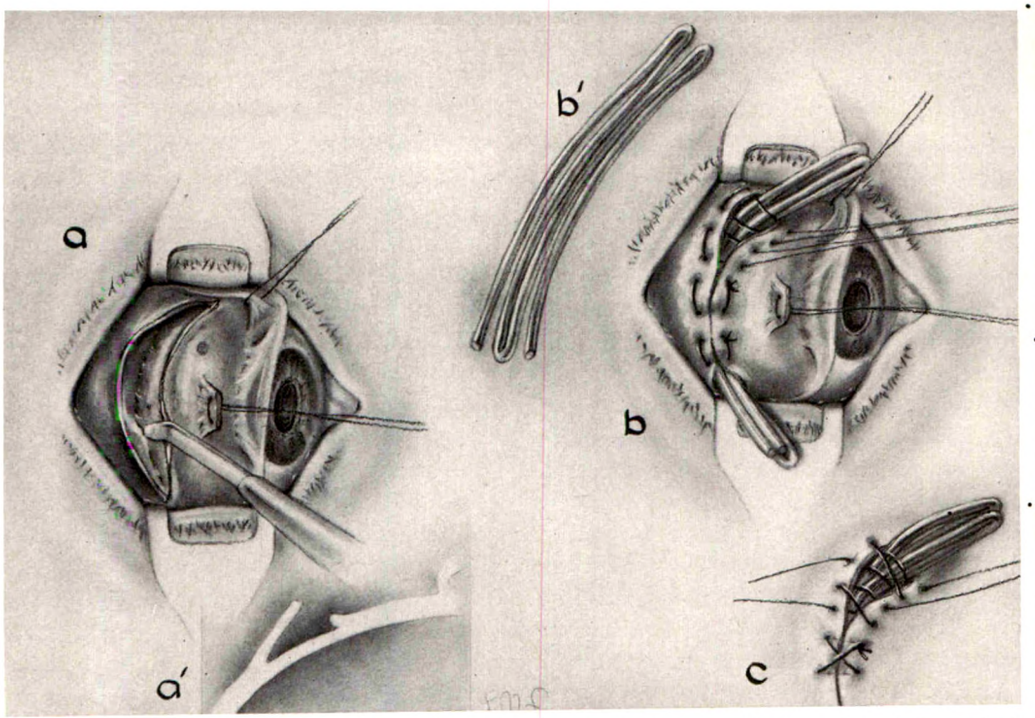



Fig. 1 (Dellaporta and Yukins). After the retinal break has been localized on the sclera, a single incision scleral groove is formed posterior to this area (a); by undermining mainly the posterior scleral lip, the groove can be placed easily behind the equator (a'); double-folded No. 2 chromic catgut (b') is enclosed within the groove (b). The mattress sutures may be the conventional U-shaped or the X type (c).

perforation. Four to five 4-0 silk mattress sutures were placed through the sceral wound edges over the groove. The overhanging scleral wound edges facilitated the safe placement of the sutures without danger of perforating the scleral wall. Additional surface or partially penetrating diathermy was placed within the bed of the scleral groove, and between both ends of the scleral groove and the ora serrata. At the present time, cryo-applications are preferred for this supplementary choroidal treatment.

Four threads of No. 2 chromic surgical catgut soaked in normal saline solution for 30 minutes were passed under the preplaced mattress sutures (Fig. 1-b).

Drainage was obtained by four to six Pischel pins inserted preferably within the scleral groove below the horizontal meridian in areas not treated with cryo-applications. The mattress sutures were pulled tight, double-looped but not knotted, burying the catgut threads within the scleral fold. In the event that this caused undesirable increase of intraocular pressure, one of the catgut threads was slipped out of the scleral fold. If ophthalmoscopic examination showed correct position of the buckle, the sutures were permanently knotted. The ends of the extruding catgut threads were cut and additional single 4-0 silk sutures were used to cover the catgut threads completely within the scleral fold. The detached muscle was resutured and the conjunctival and canthotomy wounds repaired.

## Remarks

The single-incision groove was formed well behind the retinal breaks. The aim was to have the breaks lie on the anterior slope of the buckle. This is technically easier, less time-consuming and more effective than attempting to place the breaks exactly on top of the buckle. The break positioned on the ante-

rior slope of the buckle offers an easy target for supplemental photocoagulation if this becomes necessary in the postoperative period. If ophthalmoscopic control showed the retinal breaks to be incorrectly placed, the temporarily looped mattress sutures were loosened, the posterior scleral flap was dissected further back and the buckle displaced posteriorly. No attempt was made to obtain complete drainage of the subretinal fluid. However, if the buckle was not ophthalmoscopically visible under a bullous detachment, and additional Pischel pins were of no avail, subretinal fluid was obtained by a meridionally placed scleral cut-down opposite the highest elevation of the retina. The sclera was dissected up to the choroid, the wound secured with a 4-0 single preplaced silk suture, and the choroid was perforated with a medium sized safety pin introduced tangentially (at an acute angle) into the globe and then retracted slowly as soon as subretinal fluid leaked. The blunt tip prevented perforation of choroidal vessels and possible injury to the retina in case it reached the latter. Anterior chamber paracentesis was occasionally performed to render the eye soft.

### Postoperative course

Binocular bandages were used for five to six days of bed rest, but the patients were allowed bathroom privileges and to sit up in bed during this time. Average hospitalization was eight to 10 days. The postoperative reaction and patient discomfort were similar to that seen after segmental buckling procedures using silicone rubber.

Ophthalmoscopically, the buckle diminished gradually within two to three months after surgery simultaneously with the consolidation and pigmentation of the chorioretinal scars.

### Results

Of the 21 operated eyes* only three (Cases 1, 3, and 7) were uncomplicated, prognostically favorable retinal detachments. There were 12 aphakic eyes, three had previous unsuccessful surgery, and the remainder showed some prognostically unfavorable pathology.

In two eyes (Cases 3 and 10), the buckle disappeared prematurely; in the first case, infection may possibly have caused the mattress sutures to cut through the scleral wound lips. Case 10 had an extensive juvenile detachment with atrophy of the retina and multiple ora breaks. Around the 14th postoperative day, the buckle began to diminish rapidly and increasing hypertropia was noted. Surgical exploration four weeks after the operation showed that the inferior rectus muscle, which was tenotomized during surgery, had detached and that the scleral mattress sutures had mostly cut through, leaving the scleral groove open; the enclosed catgut threads were found slightly eroded. The latter were removed, new mattress sutures were placed and pulled tight, converting the scleral groove into a single incision scleral infolding. Three months later a staphylomatous area along the operation site was repaired by a scleroplasty using preserved sclera, and the inferior rectus muscle advanced obtaining orthophoria. Both these cases were successful with resulting vision of 20/60 and 20/25, respectively. They indicate that premature disappearance of the buckle may happen as in similar procedures. If the buckle disappears after chorioretinal adhesions have formed, as probably occurred in these cases, it does not have unfavorable effects on the outcome of the operation.

Out of the 21 operations, 15 (70%) were successful within the follow-up period of seven to 18 months. Of the remaining six, in one (Case 12) the operation was unsuccessful; in three (Cases 4, 16, and 18), the detachment recurred within four to five months. These four eyes underwent successful encircling operations with a silicone rod, increasing the success rate to 89%. Two eyes (Cases 15 and 20) were unsuccessfully reoperated with the same method.

* Detailed table describing the cases may be obtained from the authors.

## Summary

The segmental scleral buckling technique with use of chromicized surgical catgut as implant offered the following advantages: Catgut is sterile and readily available; a buckle of the desired size could be easily obtained and its duration between two and three months was sufficient for curing a retinal detachment; the catgut caused a mild inflammatory reaction of the overlying choroid which promoted the formation of a contiguous area of chorioretinal adhesions between diathermy and cryo-applications.

The hydrated chromic surgical gut was a soft pliable material, did not cause pressure necroses of the structures of the eye, and finally absorbed leaving an undistorted eye. The possibility of late infections and late erosions through the sclera or conjunctiva was eliminated.

The method proved technically simple, brief, and caused little damage to the sclera. The results were as favorable as those obtained with more radical procedures.


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# SEGMENTAL RETINAL PERIARTERITIS

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Segmental periarteritis of the retina, a rare condition, is characterized by the appearance of whitish segmented plaques scattered along the retinal arteries. In most cases, an associated mild uveitis and hyalitis produce aqueous and vitreous haze, keratic precipitates, and vitreous floaters. Active or healed chorioretinal foci are frequently found near the involved vessels. It has been reported that Jensen's juxtapapillary chorioretinitis may also accompany the periarteritis.

Segmental periarteritis of the retina occurs most frequently in young adults, the average age being 34 years. It has a male/female ratio of 1.7:1. In 64.5% of cases, the condition is unilateral, the right eye being involved about 1.5 times more frequently than the left. The disease has a favorable prognosis. Within a few months, the arterial plaques disappear and recovery is complete.

Peters[1] reported the first case of segmental periarteritis of the retina in 1929. Between 1933 and 1969, 36 additional cases appeared in the literature.[2-23] If one were to include those cases in which severe uveitis, periphlebitis, or generalized vasculitis overshadowed the periarterial manifestations, those in which the course was unfavorable, or those in which the periarteritis was a localized manifestation of a systemic vascular disease (as in periarteritis nodosa), the number of cases would be greatly augmented.

This paper describes a typical case of periarteritis of the retina that showed some unusual clinical aspects, particularly in the vascular patterns demonstrated by fluorescein angiography.

## CASE REPORT

A 26-year-old man, a mason, sought treatment because of blurred vision in both eyes of eight days' duration. On admission, the anterior segment was normal in both eyes. There was slight vitreous haze and some vitreous floaters.

Examination of the fundi with the ophthalmoscope, the slit lamp, and the Goldmann lens revealed segmented, yellowish-white plaques scattered along the main arterial branches, often in a ring-like arrangement (Fig. 1). A thorough biomicroscopic examination clearly showed that the plaques adhered to the vessel walls, thereby demonstrating the classic periarterial deposition. Although segmented plaques were not seen in the smaller arterial branches, some sections showed a continuous white sheathing of the arterial walls. The caliber and the course of the arterioles were normal, but the veins appeared to be markedly enlarged and showed some segmental narrowing (Fig. 1). The optic disk appeared to be normal and the macular region somewhat edematous and blurred. Even at the extreme periphery of the fundus, no peripheral foci of chorioretinitis could be detected. The fundus findings in the right eye were not significantly different from those in the left eye.

The visual acuity, with a small hypermetropic correction, was 4/10 in the right eye and 6/10 in the left. The intraocular pressure was normal. Visual field examination with the Goldmann perimeter and the Bjerrum campimeter revealed some irregular central and paracentral relative scotomas. Dark adaptation with the Goldmann adaptometer and the electroretinographic tracing were both normal.

Fluorescein angiography showed decreased velocity of the retinal blood flow in both the arterial and the venous phases. Two minutes after the injection, the arterioles still showed fluorescence, and the veins fluoresced for more than six minutes. Some impregnation of the vascular walls with the dye could be responsible for this.

During angiography, the arterioles looked normal. The segmented white plaques seen ophthalmoscopically were not evident in the angiograms (Fig. 2). Fluorescein did not leak from the arterioles. The veins appeared to be greatly enlarged, and their walls showed a peculiar fluorescent soakage. Some extravasation of the dye became apparent about 100 seconds after the injection and lasted for more than 30 minutes (Fig. 2).

Detailed laboratory investigations, performed just after the patient's admission, gave the following results: hemoglobin, 107%; erythrocytes, 4.6 million; leukocytes, 8000 (neutrophils, 68%; lymphocytes, 27%; monocytes, 5%); glycemia, 98 mg%; azotemia, 31 mg%; blood cholesterol, 176 mg%; antistreptolysin titer, 400 units/ml; C-reactive protein, positive; serum proteins, 7.82 g%; fractionation by paper electrophoresis, normal; lipoprotein $\beta/\alpha$ ratio, 2:3. Urine was normal; erythrocyte sedimentation rate, 1-hour:4, 2-hour:8. Tests for rheumatoid arthritis, lupus erythematosus, the Wassermann and the Mantoux reaction were all negative.

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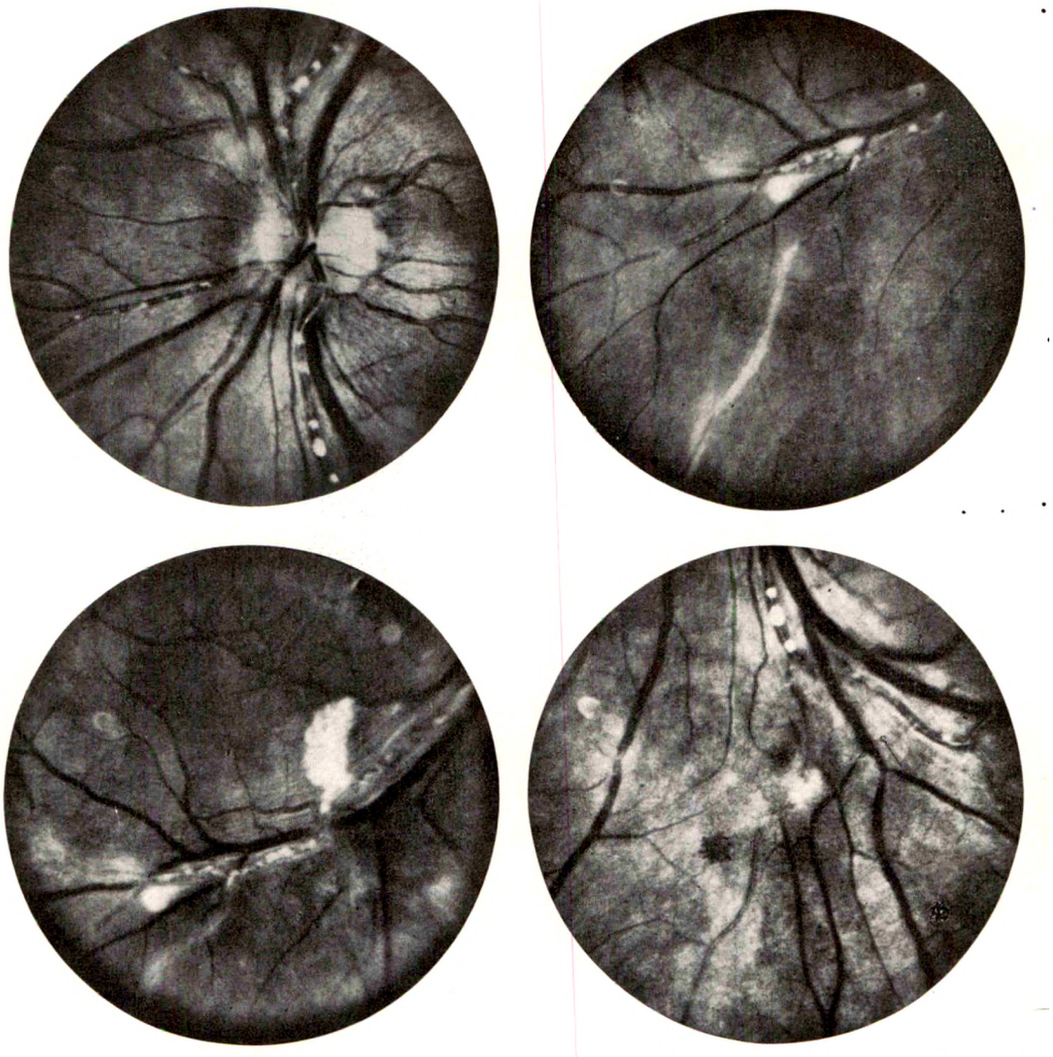


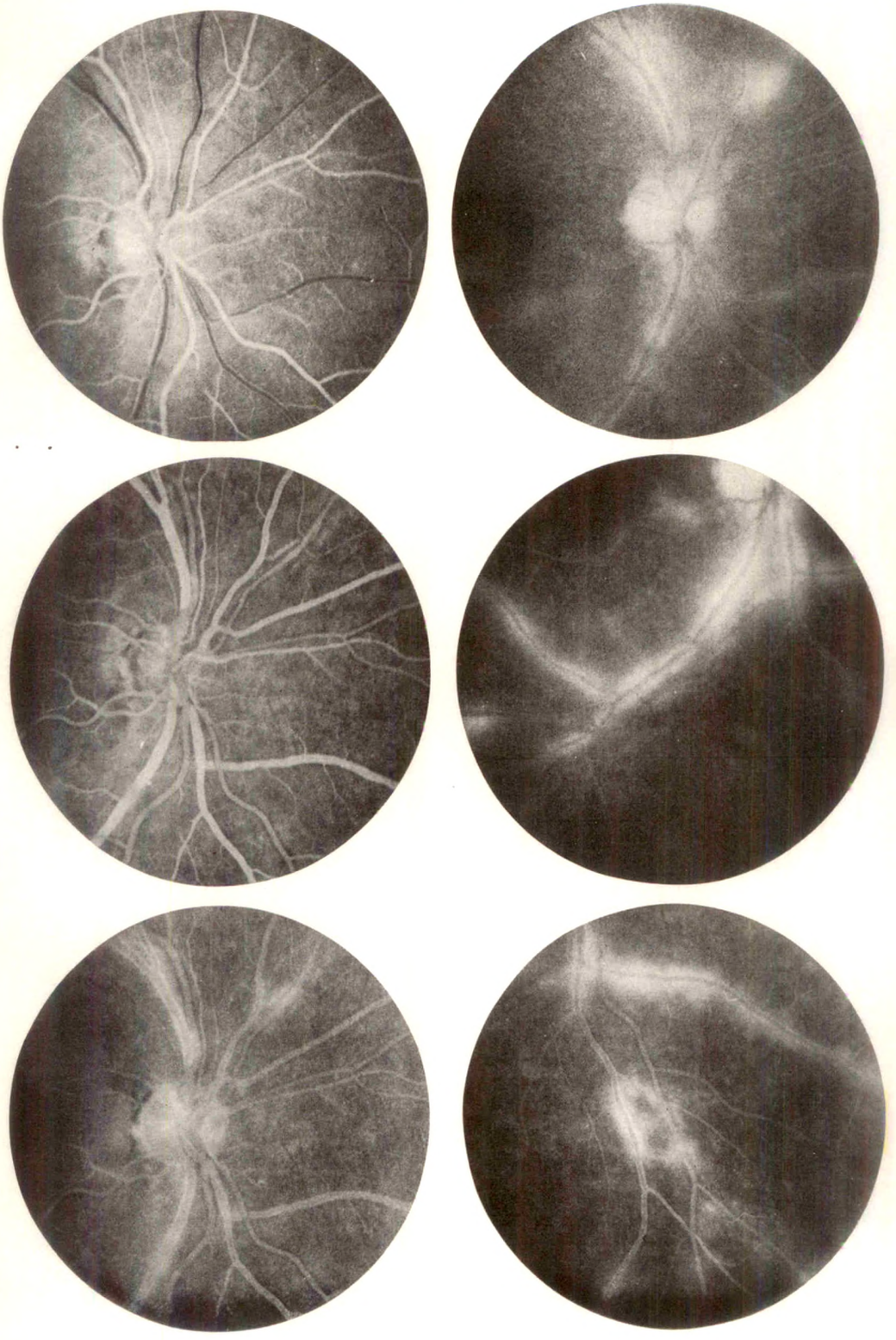
Fig. 1 (Orzalesi and Ricciardi). Ophthalmoscopic aspects of segmental periarteritis of the retina. Top left: Plaques of periarteritis ensheathing the large arterial branches. Top right: Continuous sheathing of the small arterial branches. Bottom left: Exudates. Bottom right: Hemorrhages observed during the period of recovery from segmental periarteritis of the retina.

General physical examination showed acute rhinitis, chronic tonsillitis, and gingivitis, as well as numerous dental caries. The neurologic examination disclosed no abnormality. Chest roentgenograms were normal but sinus films showed maxillary sinusitis. Oscillography of the arms and legs gave normal findings. Histologic examination of a temporal artery biopsy detected no disease.

The patient received intensive antiobiotic (streptomycin and tetracycline) and corticosteroid therapy, including intraorbital injections of dexamethasone. Fifteen days after initiation of therapy, the



Fig. 2 (Orzalesi and Ricciardi). Florescein angiography of segmental retinal periarteritis, showing the arterial and venous phases (left) and the late venous phases (right). During the venous phase, hyperfluorescence of the vein walls and leakage of the dye are clearly seen.



patient's eyes showed marked improvement. Uncorrected visual acuity was now 8/10 in the right eye and 10/10 in the left. Reduction in the number of vitreous exudates and in the extent of the macular edema fostered the visual improvement. With the exception of a few fluffy preretinal exudates bulging from the walls of the larger arterial branches (Fig. 1), the vascular findings were practically unchanged at this time.

Visual acuity improved to 10/10 in both eyes during the following days. The scotomas disappeared completely. As the signs of periarteritis began to fade, the continuous white sheathing of the small arteries disappeared first, then the preretinal exudates and, finally, the segmented plaques ensheating the largest retinal arteries.

During the three months between the start of therapy and complete recovery, some small hemorrhages were seen near the largest vascular branches. Repeated fluorescein angiographies during this period showed decreasing involvement of the retinal veins. The angiographic picture was again normal about one month after admission.

The marked decrease in the fluorescence of the retinal vessels that also occurred during recovery might have been produced by the healing process effecting a decrease in the transparency of the vascular walls.

Laboratory investigations showed that removal of the antral, dental, and tonsillar foci of infection by the antibiotic and corticosteroid therapy had normalized the antistreptolysin titer and the C-reactive protein.

## Discussion

Segmental periarteritis of the retina is a well-established clinical entity. The prevalence of segmental lesions of the retinal arteries, the principal feature of the clinical picture, the mild associated ocular signs, and the favorable clinical course separate this condition from others in which periarteritis occurs as an inconstant and secondary finding—for example, as in cases of uveitis with perivasculitis or in periarteritis nodosa.

Appelman and associates[13] and François and co-workers[21] discussed the etiology of segmental periarteritis of the retina at length. Since arteriosclerosis,[15] periarteritis nodosa,[24] and herpes[25] have none of the characteristics of segmental periarteritis of the retina, they can be excluded from etiologic consideration.

It seems more probable that most of the reported cases had an allergic etiology. The segmental changes in the retinal arteries could result from an immune reaction to a bacterial antigen or even to drugs.[22] The tonsillar, dental, and antral foci of infection, the increase in the antistreptolysin titer, and the positive C-reactive protein test in our patient indicate an allergic reaction to bacterial antigens. This patient's favorable response to intensive antibiotic and corticosteroid therapy support this contention.

An unusual aspect of this case was involvement of the retinal venous system, as shown by fluorescein angiography. This patient differed from those reported previously[21,22] in whom angiography demonstrated no abnormalities. The angiographic demonstration of hyperfluorescence of the vessel wall and seepage of the dye in patients with inflammatory cells in the vitreous, as in the present case, may be interpreted as evidence of retinal vasculitis and perivasculitis.[26]

A similar angiographic picture can also be observed in other conditions affecting the retinal veins, such as retinal vein obstruction, Eales' disease, and diabetic retinopathy.

To explain the retinal phlebitis, we suggest that the same noxious reaction which induced the periarteritis also affected the vein walls and caused an ophthalmoscopically invisible mild phlebitis to become associated with the dominant changes in the arteries. Slowing of the venous blood flow and stasis in the capillary and arterial network could facilitate formation of the arterial lesions.[15,27] Without fluorescein angiography, vascular alterations as vasculitis and perivasculitis might not be detected.

## Summary

In a typical case of segmental periarteritis of the retina, a peculiar alteration in the retinal veins was detected by fluorescein angiography that was not evident on ophthalmoscopic examination. The effectiveness of intensive antibiotic and corticosteroid therapy in erradicating the antral, dental, and tonsillar foci of infection suggests that an allergic reaction to bacterial antigens was the etio-

logic factor in this case. Three months after onset, the patient was cured.

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# RHYTHMIC WAVELETS OF THE POSITIVE OFF EFFECT IN THE HUMAN ELECTRORETINOGRAM

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The human electroretinogram (ERG), evoked with intense illumination, presents a sequence of rhythmic wavelets superimposed on the rising phase of the b-wave.[1,2] Similar rhythmic on wavelets are found in many vertebrates and are labeled the "oscillatory potentials.[3]" Studies of the nature of these oscillatory potentials[3-6] demonstrated their clinical importance.[7-9] Other studies demonstrated that the positive off effect is also divided into multiple peaks in frog,[10-13] turtle,[14] pigeon,[15-16] and human.[17-20] Because of technical and other problems resulting from their low amplitudes, the off effect and its subcomponents have not been closely examined in the human. This paper demonstrates how multiple off effects in man are easily recorded, using intense stimuli, an averaging computer, and short-time constant amplifier.

## METHOD

The stimulus light was derived from a tungsten lamp (1 kw, 100 v) passed through a series of heat and neutral density filters and brought to a focus at a magnetic shutter. Square-wave test flashes (stimulus duration 740 msec 0.7 Hz) were delivered from the shutter, driven by an electronic stimulator.

The adapting light was provided by another tungsten lamp (150 w, 117 v), also controlled by a series of heat and neutral density filters.

Stimulus and adapting lights were focused on each of the two input ends of a dichotomic (Y-shaped) glass fiber light guide. The glass fibers carrying the light from each source were mingled together at the output end (7 mm in diameter), which was held 2 cm from the cornea of the subject's eye. The intensity of the stimulus light without neutral density filter was $2.9 \times 10^3$ ft-L ($6.3 \times 10^5$ scotopic trolands, pupil diameter 7.5 mm). The maximum adapting light intensity was $1.8 \times 10^3$ ft-L ($4.0 \times 10^5$ scotopic tds.). Neutral density filters were interposed in the light path to decrease the luminance. Stimulus and adapting light intensities are represented in $\log_{10}$ units and they are directly comparable. The maximum stimulus intensity ($2.9 \times 10^3$ ft-L) is designated as 0.0 log units, the maximum adapting intensity ($1.8 \times 10^3$ ft-L) therefore corresponds to $-0.2$ log units.

In this study, with an averaging computer we used repetitive stimuli (740 msec duration) of 0.7 Hz which will cause a degree of light adaptation. This adapting effect was considered by matching (a) the amplitudes of b-waves evoked by repetitive stimuli with no background light and (b) the amplitude of b-wave evoked by a single flash with at constant levels of light adaptation. With our stimulus duration and frequency we found, for example, that repetitive stimuli of $-3.0$ log units produced a light adapting effect equivalent to a steady state adapting light intensity of about $-6.0$ log units, and repetitive stimuli of $-1.0$ log units produced about $-2.0$ log units of adapting light effect. Therefore, the term "with no adapting light" or "in the dark," as used in this paper, does not mean the fully dark-adapted state.

ERG potentials were detected with a low vacuum contact lens electrode,[21] referred to the combined earlobes, and led to a Grass EEG amplifier (7P511). Fifty or 100 re-

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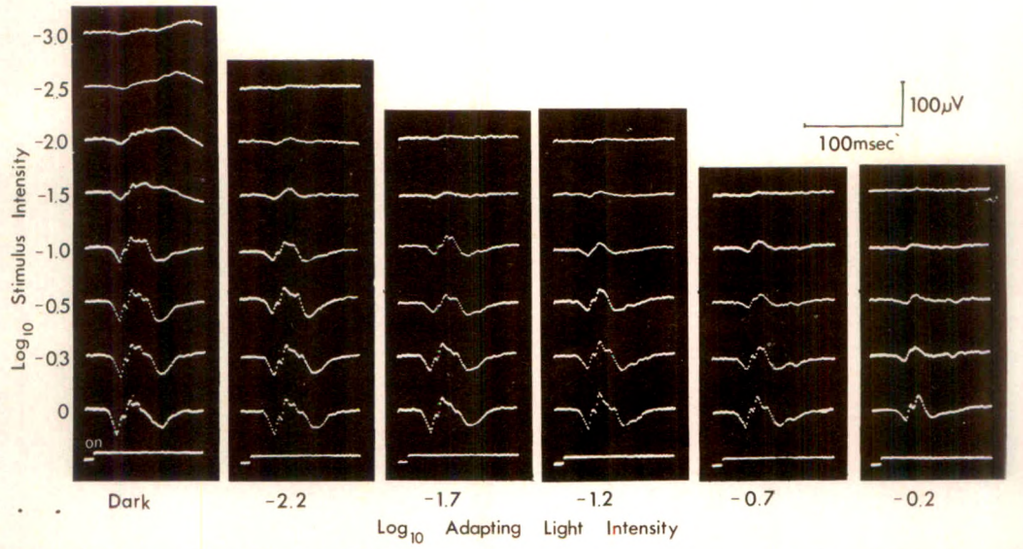



Fig. 1 (Tsuchida, Kawasaki, and Jacobson). On effects of the normal human ERG at varying levels of stimulus and adapting light intensities. Stimulus duration 740 msec. Stimulus frequency 0.7 Hz. Time constant 0.01 sec. Upward deflection indicates positivity of corneal electrode. Average of 50 responses.

sponses were averaged by a Mnemotron compute (CAT 400). The amplifier time constant is specified in each figure.

The normal data collected by one of us (K. K.) was confirmed by other normal subjects, including subjects under general anesthesia. Pupils were fully dilated with 1% tropicamide. The cornea was anesthetized with 0.5% tetracaine. Subjects were instructed to try not to blink and not to move the eye during recording. When the ERG was obviously contaminated by artefact due to blinking or other muscle movement, data was discarded.

## Results

A weak stimulus (−3.0 log units) evoked only a positive potential (b-wave) with no background light (Fig. 1). As the stimulus intensity was increased, a small negative deflection (a-wave) and a series of on wavelets (oscillatory potentials) superimposed on the b-wave, were recordable and their amplitudes increased progressively with increasing stimulus intensity. These oscillatory potentials are conventionally labeled $0_1$, $0_2$, $0_3$, and $0_4$ (Fig. 2-A).

With no background light, as stimulus intensity was increased to −2.5 log units, the positive off effect became recordable (Fig. 3). More intense stimuli made the positive off effect prominent and its initial ascending slope steeper. At maximum stimulus intensity (0.0 log units), the latency and the peak latency of the initial positive off effect were about 10 and 21 msec, respectively.

The positive off effect is divided into three main peaks when the stimulus is brighter than −1.0 log units. We call them $d_1$, $d_2$, and $d_3$ for the convenience of description (Fig. 2-B). However, $d_3$ was absent in all three normal subjects under general anesthesia, and not always present in conscious normal subjects. $D_3$ might be an artefact due to blinking or other muscle movement. It is also possible that general anesthesia might eliminate $d_3$. Because of these ambiguities, we will not further treat $d_3$ in this paper.

With intense stimulus, fast rhythmic wavelets were superimposed on $d_1$ and $d_2$. These fast off wavelets were observed in all normal subjects tested, and their inverted shape resembled that of the oscillatory potentials

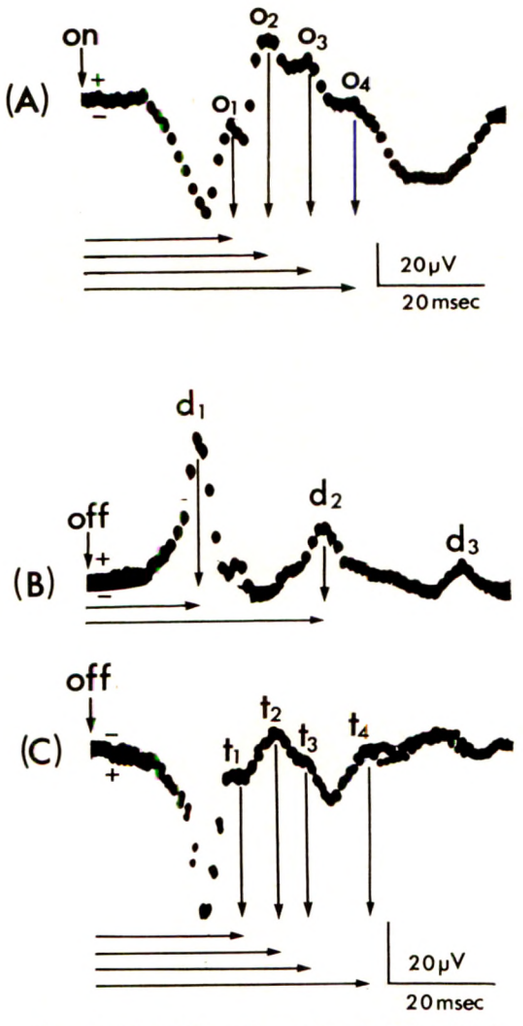



Fig. 2 (Tsuchida, Kawasaki, and Jacobson). Sample records of on (A) and off effects (B, C). Upward deflection indicates positivity of the corneal electrode in traces A and B, and negativity in trace C. Two responses to same stimulus were superimposed in trace C. Oscillatory potentials ($O_1$-$O_4$), $d_1$-$d_3$ waves and troughs of the off wavelets ($t_1$-$t_4$) are designated. Note that troughs of the off wavelets ($t_1$-$t_4$) correspond to peaks of oscillatory potentials ($O_1$-$O_4$). Stimulus intensity 0.0 log units. No background light. Stimulus duration 740 msec. Stimulus frequency 0.7 Hz. Time constant 0.01 sec. Average of 50 responses.

superimposed on the b-wave. Figure 2-C presents the off effects in reversed polarity to facilitate comparison of its waveform with that of the on effect. We call the negative peaks of the fast off wavelets as "troughs" of off wavelets ($t_1$, $t_2$, $t_3$, and $t_4$) for the convenience of description.

The amplitudes and the peak latencies of the on and off components recorded with no background light are plotted against stimulus intensity (Figs. 4 and 5). The amplitudes of the oscillatory potentials ($O_1$-$O_4$) were measured from the bottom of the a-wave (Fig. 2-A). The amplitude of $d_1$ was measured from the baseline and that of $d_2$ from the negative trough between $d_1$ and $d_2$ (Fig. 2-B). The amplitudes of the troughs of the off wavelets ($t_1$-$t_4$) were measured from the peak of $d_1$ (Fig. 2-C).

The amplitudes of the a-wave and the oscillatory potentials increased linearly to the log stimulus intensity within the stimulus range tested (Fig. 4-A). The amplitudes of $d_1$, $d_2$ and troughs of the off wavelets increased approximately linearly to log stimulus intensity (Fig. 4-B). The threshold (10 μv criterion) of $d_1$ is about 0.8 log units lower than that of $d_2$. A gross parallelism exists between the amplitudes of a-wave and $d_1$ (Figs. 4-A and B).

The peak latencies of the a-wave and the oscillatory potentials decreased slightly as the stimulus intensity increased, but the intervals between the individual peak of the oscillatory potentials underwent no remarkable change (Fig. 5-A). The peak latencies and, hence, the intervals between successive waves of $d_1$, $d_2$, $t_1$, $t_2$, $t_3$ and $t_4$ remained fairly stable regardless of stimulus intensity (Fig. 5-B).

Varying the level of light adaptation through the range of $-2.2$ to $-0.2$ log units did not alter these findings (Figs. 4 and 5).

The amplitudes and the peak latencies of the on and off components recorded with maximum stimulus intensity (0.0 log units) are plotted against adapting light intensity (Figs. 6 and 7).

The amplitudes of the a-wave, $O_3$ and $O_4$ decreased as the light adaptation level increased (Fig. 6-A). The amplitude of $O_1$ was little affected by adapting light and that of

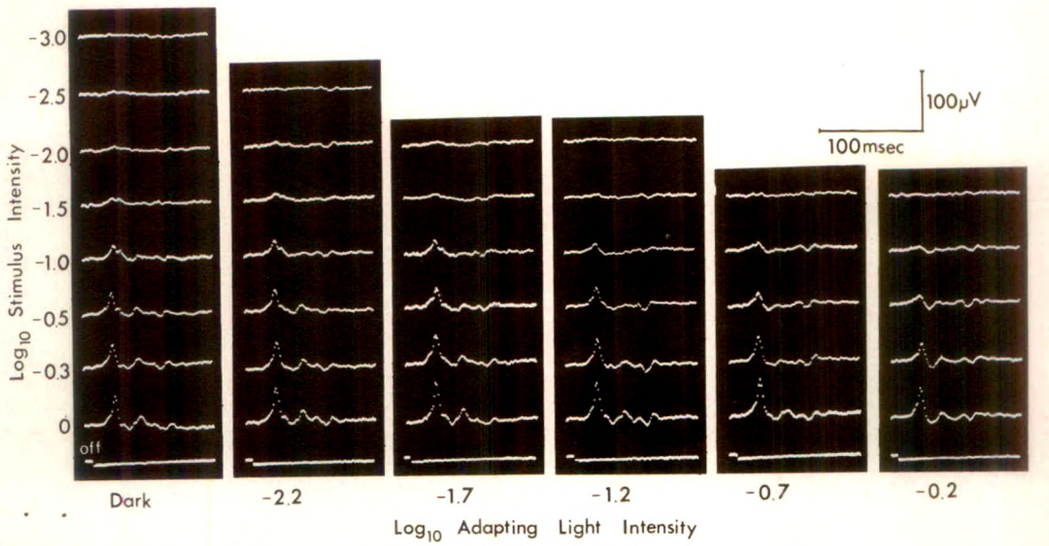



Fig. 3 (Tsuchida, Kawasaki, and Jacobson). Off effects of the normal human ERG at varying levels of stimulus and adapting light intensities. Recording conditions same as Figure 1.

$0_2$ was augmented with increasing adapting light intensity, up to −1.2 log units, beyond which it decreased. The amplitudes of $d_1$ and $d_2$ increased slightly with a weak adapting light (−2.2 to −1.7 log units), as compared with their amplitudes with no background light (Fig. 6-B). When adapting light intensity was increased to maximum intensity (−0.2 log units), the amplitude of $d_1$ remained almost the same as in the dark, while the amplitude of $d_2$ was reduced to about two-thirds of the original value. The amplitudes of the troughs of the off wavelets gradually increased as the adapting light intensity was increased, up to −1.7 log units, then decreased.

The peak latencies of the a-wave and the oscillatory potentials were slightly prolonged as the light adaptation level was increased (Fig. 7-A). The peak latencies of $d_1$, $d_2$, and the troughs of the off wavelets remained almost constant throughout the entire range of light adaptation tested (Fig. 7-B).

The entire ERG response, including the oscillatory potential and off wavelets, was extinguished in a case of primary pigmentary degeneration of the retina in a 57-year-old woman (Fig. 8-A). The amplitudes of the a- and b-waves were moderately decreased in a case of diffuse chorioretinal degeneration in a two year-old girl under general anesthesia. The oscillatory potential and off wavelets of this patient were almost absent (Fig. 8-B). The amplitudes of the a- and b-waves were moderately decreased in a case of chloroquine retinopathy in a 36-year-old woman (total dosage of hydroxychloroquine, 182 g). In this case, both the oscillatory potential and off wavelets were markedly decreased (Fig. 8-C). In a case of diabetic retinopathy (a 64-year-old woman, severe in left eye and somewhat less severe in right eye), the amplitudes of the a- and b-waves were greatly decreased in the left eye and almost normal in the right eye. Both the oscillatory potential and off wavelets of this patient were decreased to the same extent (Figs. 8-D, E). The normal ERG response, including the oscillatory potential and off wavelets, was obtained in a case of optic nerve atrophy in a four-year-old boy under general anesthesia (Fig. 8-F).

## Discussion

Heck[17] described the multiple off effects as "doppelte positive Off-Effekt," referring to the first and second off effects. His first

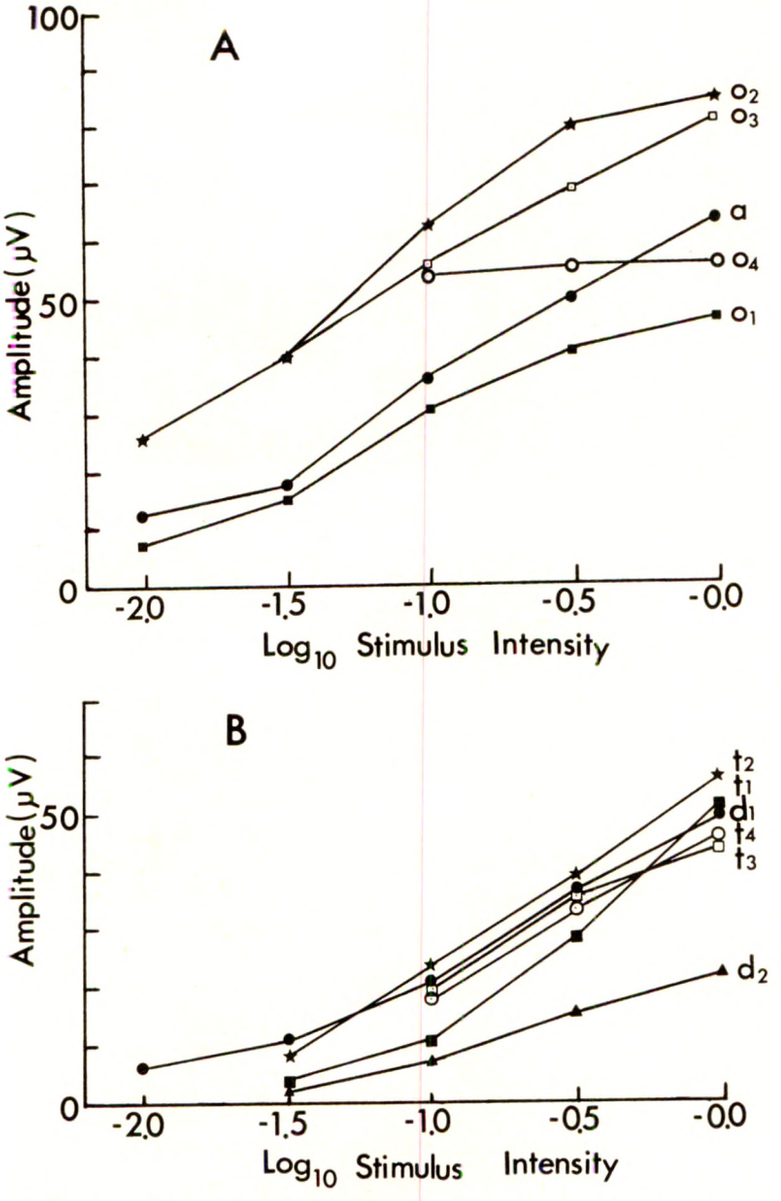



Fig. 4 (Tsuchida, Kawasaki, and Jacobson). Amplitudes of oscillatory potentials (A), and multiple off effects (B) as function of stimulus intensity. Amplitudes of these potentials were calculated from the data with no background light. Note that amplitudes of all responses increase linearly to log stimulus intensity.

and second off effects would seem to correspond to our $d_1$ and $d_2$, respectively (Fig. 2-B). He attempted to relate the first and second off effects to photopic and scotopic components, respectively.

In considering this concept, one must recognize that: (1) The threshold of $d_2$ is higher than that of $d_1$ (Fig. 4). (2) $D_2$ was present, although of slightly less than maximum amplitude, under our maximum adapting light intensity ($-0.2$ log units, $4.0 \times 10^5$ scotopic tds), which is strong enough to

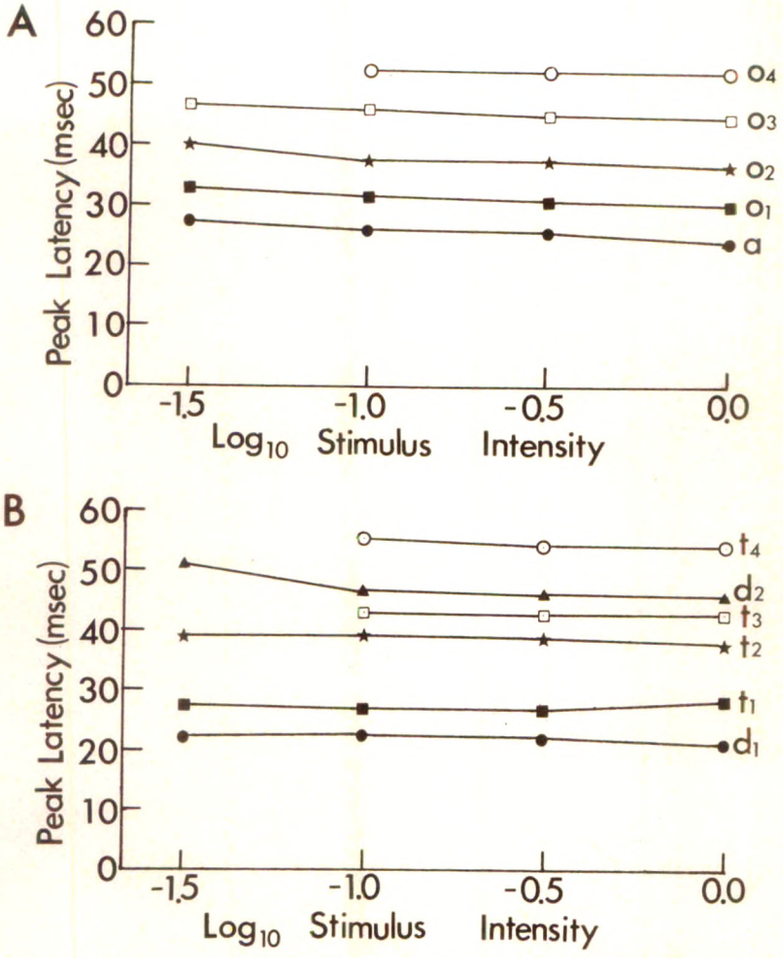



Fig. 5 (Tsuchida, Kawasaki, and Jacobson). Peak latencies of oscillatory potentials (A) and multiple off effects (B) as function of stimulus intensity. Latencies calculated from data with no background light. Note constancy of intervals between oscillatory potentials and troughs of off wavelets, regardless of stimulus intensity.

saturate the human rod system (2000 to 5000 scotopic tds).[22] (3) In stationary congenital night blindness, $d_2$ was recordable.[19,20] (4) $D_2$ has been recorded in the pigeon, which has a pure cone fovea and a cone-dominated peripheral retina,[23] and was highly resistant to light adaptation.[15] These facts do not support the assumption that $d_2$ is indicative of scotopic function.

It has been suggested that the off effect is a mirror image of the on effect.[17,24] The troughs of the off wavelets ($t_1$, $t_2$, $t_3$, and $t_4$), resemble the oscillatory potentials ($0_1$, $0_2$, $0_3$ and $0_4$) in the following points: (1) The threshold of both wavelets are relatively high and approximate each other, although the thresholds of the oscillatory potentials are slightly lower (Fig. 4). (2) The peak latencies of the individual oscillatory potentials and those of the troughs of the off wavelets approximate each other, and their intervals are stable regardless of the stimulus and adapting parameters (Figs. 5 and 7). (3) Both oscillatory potentials and off wavelets, and especially their early portion, are highly resistant to light adaptation (Fig. 6).

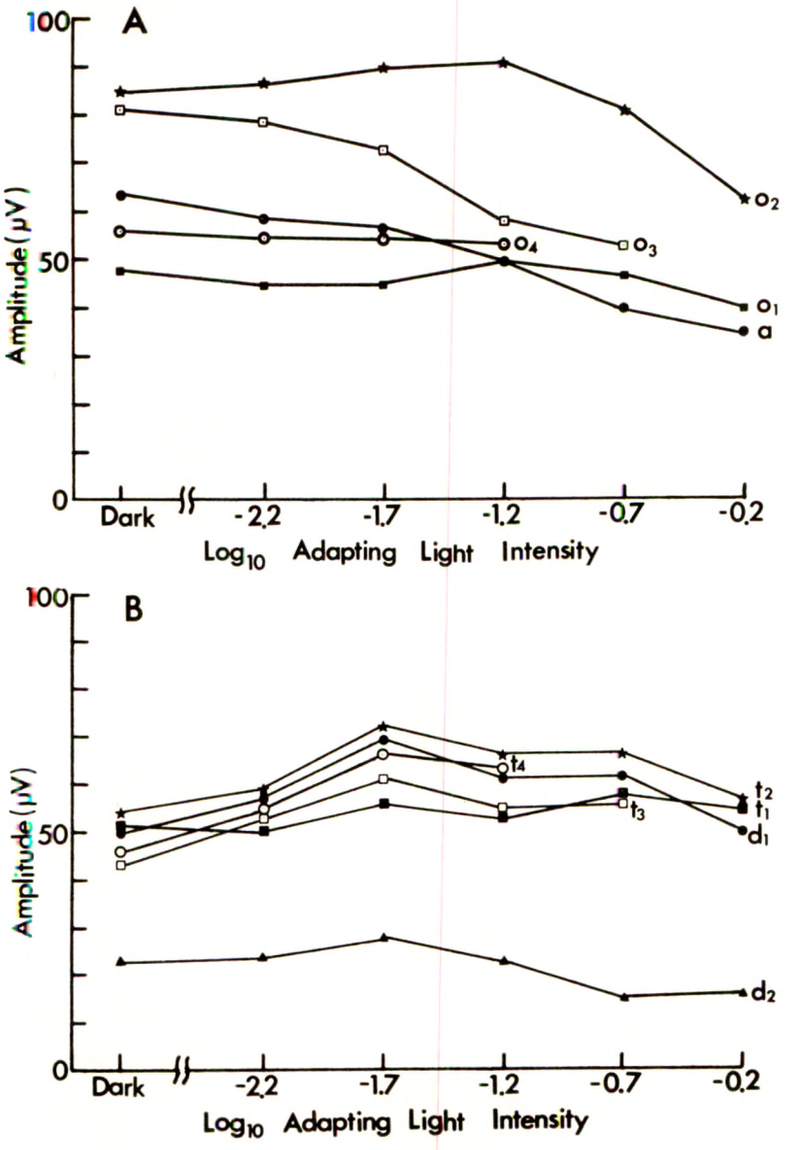



Fig. 6 (Tsuchida, Kawasaki, and Jacobson). Amplitudes of oscillatory potentials (A) and multiple off effects (B) as function of adapting light intensity. Curves obtained from data with maximum stimulus intensity (0.0 log units).

(4) Both oscillatory potentials and off wavelets are equally diminished in retinal diseases we studied (Fig. 8). There are, however, some differences between the oscillatory potentials and the off wavelets: (1) The troughs of the off wavelets, especially $t_3$, are not as prominent as the oscillatory potentials. (2) The intervals between the troughs of the off wavelets are not as regular as those of the oscillatory potentials.

According to Brown's analysis of the mammalian cone ERG,[6] the positive off effect is composed of two different components of opposite polarity; the onset phase appears to result from decay of the cone receptor potential, while the falling phase appears to re-

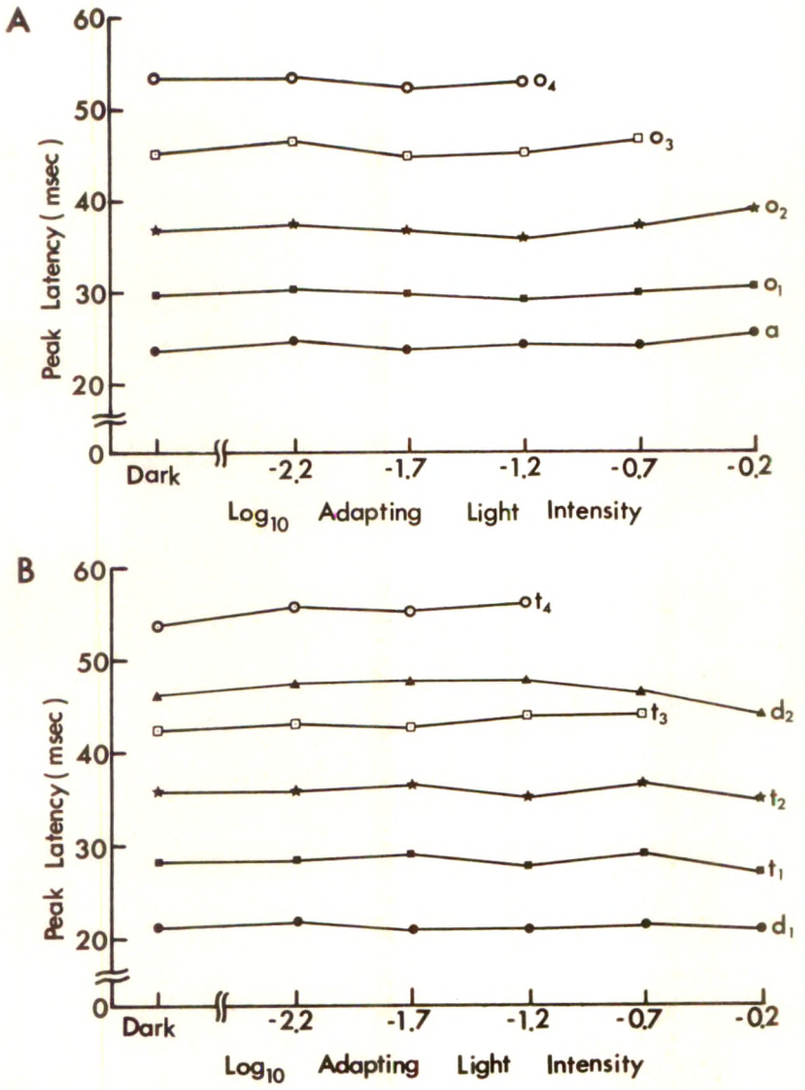



Fig. 7 (Tsuchida, Kawasaki, and Jacobson). Peak latencies of oscillatory potentials (A) and troughs of off wavelets (B) as function of adapting light intensity. Curves obtained from data with maximum stimulus intensity (0.0 log units). Note constancy of intervals between individual oscillatory potentials and troughs of off wavelets, regardless of adapting light intensity.

sult from decay of the d.c. component. Off wavelets are not considered in his analysis, although he did describe the oscillatory potential as one of the minor components of the ERG. The off wavelets must be considered as a new component of the ERG.

The origin of the oscillatory potentials has been inferred to be at the bipolar cell layer.[3-5,7,25] The many similarities between the oscillatory potentials and the off wavelets make it conceivable that the origin of the off wavelets is also in the bipolar cell layer.

## Summary

Intense stimuli of 740 msec duration evoked a sequence of fast rhythmic wavelets superimposed on the positive off effect. These off wavelets were observed in all nor-

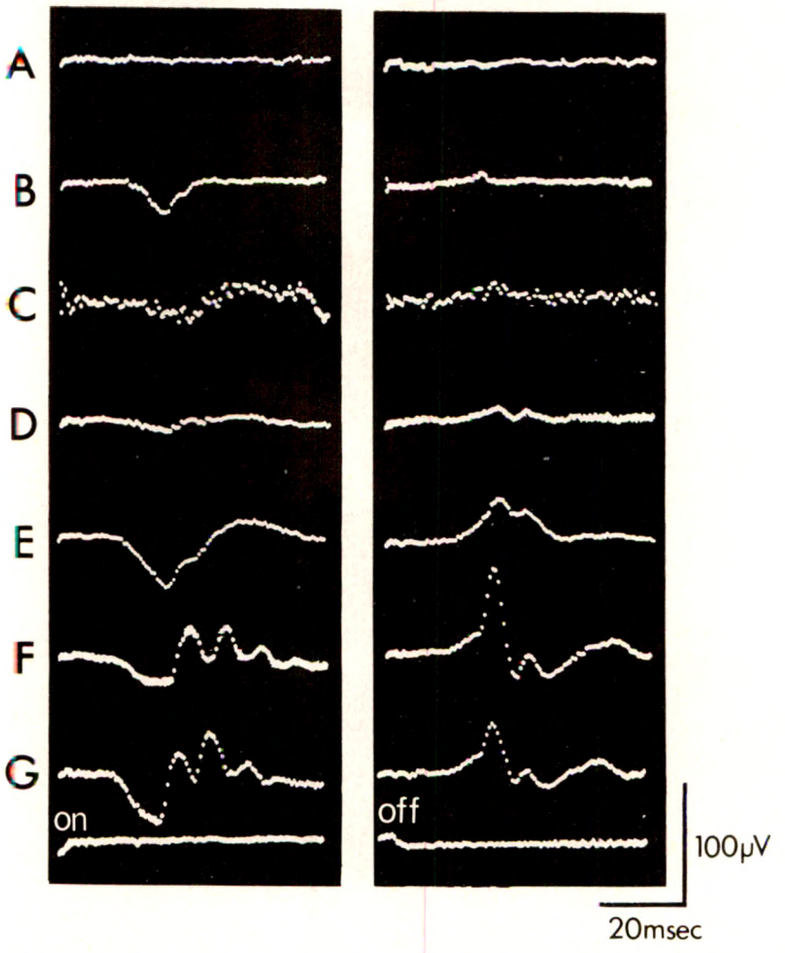



Fig. 8 (Tsuchida, Kawasaki, and Jacobson). Oscillatory potentials and off wavelets in pathologic cases. (A) Primary pigmentary degeneration, (B) diffuse chorioretinal degeneration, (C) chloroquine retinopathy, (D and E) diabetic retinopathies (Scott III and II), (F) optic nerve atrophy, and (G) normal control. Stimulus intensity 0.0 log units. No background light. Stimulus duration 740 msec. Stimulus frequency 0.7 Hz. Time constant 0.003 sec. Upward deflection indicates positivity of corneal electrode. Average of 100 responses.

mal subjects tested, and their shape, inverted, resembled that of the oscillatory potentials superimposed on the b-wave. Close similarity exists in amplitude and latency from stimulus off and on, respectively, between the troughs of the off wavelets and the peaks of the oscillatory potentials. Studies of several pathologic cases indicated gross parallelism in effects upon the off wavelets and upon the oscillatory potentials in the diseases in question.

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# OCULAR PIGMENTATION AND PRESSURE AND OUTFLOW RESPONSES TO PILOCARPINE AND EPINEPHRINE

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In 1929 Chen and Poth[1] compared the pupil dilating effect of several mydriatics (cocaine, euphthalmine, ephedrine) in Caucasians, Chinese, and Negroes. They found that Caucasians were the most responsive, Negroes the least, and Chinese intermediate to the mydriatic action of these drugs. Scott[2] has reported similar racial differences.

Studies by Howard and Lee[3] and Guist[4] have also demonstrated that mydriatics are more effective in individuals with light irides than in those with dark.

There has been no conclusive evidence as to whether the degree of responsiveness is racially determined or secondary to the quantity of pigmentation. It does, however, point out a specific pattern for drug response variation.

The purpose of this study was to determine if the quantity of pigmentation in the skin, iris, trabecular meshwork, or fundus could be correlated to the intraocular pressure response to pilocarpine or epinephrine.

## MATERIALS AND METHODS

Twenty-three women volunteers between the ages of 20 and 40 years were given complete eye examinations by one investigator. Subjects were disqualified for the following reasons: (1) a history of systemic or ocular disease, (2) a history of eye trauma, (3) a present history of drug therapy except for oral contraceptives, (4) physical evidence of previous ocular inflammation, iris atrophy, pigment dispersion, lens pseudoexfoliation or chamber angle abnormalities, or (5) a spherical refractive error of three diopters or more, or a cylindrical error of one diopter or more.

During the first visit the pigmentation of the volar forearm skin, iris, trabecular meshwork, and fundus was evaluated visually. The skin pigment was recorded as light, medium, and heavy. The irides and fundi were described by color. The trabecular meshwork was graded as translucent, or with light, medium, or heavy pigmentation.

As a check, photographs of the volar forearm skin, iris, trabecular meshwork, and fundus of each subject were taken under standardized conditions. These were later compared with the recorded visual evaluations. If there was a discrepancy between the written and photographic evaluation, the subject was re-examined visually and this evaluation was considered as final.

At the second visit, each volunteer underwent Goldmann applanation tonometry and tonography on both eyes. Immediately upon completion of the tonography, one drop of 4% pilocarpine was instilled in the lower fornix of the right eye. The subject was requested to blink for several seconds and then sit with eyes open. Approximately 15 to 30 seconds later a second drop was instilled in the right eye. After a few blinks both eyes were kept closed for five minutes. The subject was then allowed to leave, but told to return in exactly two hours at which time applanation tonometry and tonography were repeated on both eyes.

About two weeks later this same procedure was again followed except the pilocarpine was instilled only in the left eye.

During the fourth and fifth visits the same format was again followed except that 2%

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TABLE 1

AVERAGE CHANGES IN PRESSURE AND FACILITY OF OUTFLOW IN NORMAL EYES TWO HOURS AFTER TREATMENT WITH 4% PILOCARPINE COMPARED WITH AVERAGE CHANGES IN UNTREATED EYES

| Category | | Lightly Pigmented | | | | Heavily Pigmented | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. Eyes | Δ Tap (mm Hg) | Δ $P_0$ (mm Hg) | ΔC (μl/ minute/ mm Hg) | No. Eyes | Δ Tap (mm Hg) | Δ $P_0$ (mm Hg) | ΔC (μl/ minute/ mm Hg) |
| Skin: | Treated eye | 21 | −2.6 | −3.2 | +0.06 | 11 | −1.1 | −1.9 | +0.02 |
| | Untreated eye | | −1.0 | −1.4 | −0.02 | | −0.8 | −0.9 | +0.00 |
| | Difference | | −1.6 | −1.8 | +0.08 | | −0.3 | −1.0 | +0.02 |
| | Significance | | S* | S | S | | NS† | NS | NS |
| Iris: | Treated eye | 15 | −2.5 | −3.1 | +0.08 | 18 | −2.0 | −2.6 | +0.06 |
| | Untreated eye | | −1.2 | −1.3 | −0.02 | | −0.8 | −0.8 | −0.02 |
| | Difference | | −1.3 | −1.8 | +0.10 | | −1.2 | −1.8 | +0.08 |
| | Significance | | S | S | S | | NS | S | NS |
| Trabecular meshwork: | Treated eye | 16 | −2.6 | −3.0 | +0.05 | 15 | −1.5 | −2.0 | +0.04 |
| | Untreated eye | | −1.0 | −1.2 | −0.04 | | −0.5 | −0.8 | −0.03 |
| | Difference | | −1.6 | −1.8 | +0.09 | | −1.0 | −1.2 | +0.07 |
| | Significance | | S | S | S | | NS | NS | NS |
| Fundus: | Treated eye | 13 | −2.5 | −3.4 | +0.08 | 17 | −2.1 | −2.7 | +0.03 |
| | Untreated eye | | −1.0 | −1.7 | −0.03 | | −1.1 | −0.6 | −0.02 |
| | Difference | | −1.5 | −1.7 | +0.11 | | −1.0 | −2.1 | +0.05 |
| | Significance | | S | S | S | | NS | S | NS |

* Significant.
† Not significant.

epinephrine was used instead of the pilocarpine.

The pre- and post-medication Goldmann applanation pressures (Tap), opening tonographic pressures ($P_0$), and outflow facilities (C) were recorded for each subject at each visit. The initial Tap, $P_0$ and C values were subtracted from the second set of values obtained two hours after treatment of the one eye.

Positive (+) Tap and $P_0$ values indicated increase in the intraocular pressures after treatment whereas minus (−) values indicated a fall in pressure. Positive (+) C values indicated an increase in the outflow facility after treatment whereas minus (−) C values indicated a decrease.

Before the final analysis of results, the medium pigmented group in each category (skin, iris, trabecular meshwork, and fundus) was discarded and only the extremes of pigmentation (light and heavy) were compared.

Using a P level of 0.05, a student's t-test for unpaired samples of unequal numbers was used for statistical evaluation comparing the treated to the untreated eyes.[5]

The average change for the treated and untreated eyes and their differences were also calculated and recorded.

## RESULTS

Table 1 shows that normal subjects with lightly pigmented skin, irides, trabecular meshwork, and fundi respond with a greater fall in intraocular pressure and increase in

TABLE 2

AVERAGE CHANGES IN PRESSURE AND FACILITY OF OUTFLOW IN NORMAL EYES TWO HOURS AFTER TREATMENT WITH 2% EPINEPHRINE COMPARED WITH AVERAGE CHANGES IN UNTREATED EYES

| Category | | Lightly Pigmented | | | | Heavily Pigmented | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. Eyes | Δ Tap mm Hg | Δ $P_0$ mm Hg | ΔC μl/ minutes/ mm Hg | No. Eyes | Δ Tap mm Hg | Δ $P_0$ mm Hg | ΔC μl/ minute/ mm Hg |
| Skin: | Treated eye | 18 | −1.8 | −0.4 | +0.06 | 10 | −0.7 | +0.4 | +0.10 |
| | Untreated eye | | −0.5 | −0.3 | −0.06 | | −0.4 | −0.8 | +0.06 |
| | Difference | | −1.3 | −0.1 | +0.12 | | −0.3 | +1.2 | +0.04 |
| | Significance | | S* | NS† | S | | NS | NS | NS |
| Iris: | Treated eye | 14 | −2.0 | −0.4 | +0.07 | 14 | −0.4 | +0.1 | +0.08 |
| | Untreated eye | | −0.7 | −0.4 | −0.05 | | −0.4 | −0.6 | +0.03 |
| | Difference | | −1.3 | 0.0 | +0.12 | | 0.0 | +0.7 | +0.05 |
| | Significance | | S | NS | S | | NS | NS | NS |
| Trabecular meshwork: | Treated eye | 14 | −1.6 | −0.7 | +0.07 | 14 | −0.7 | +1.0 | +0.08 |
| | Untreated eye | | −0.4 | −0.6 | −0.04 | | +0.1 | −0.2 | +0.01 |
| | Difference | | −1.2 | −0.1 | +0.11 | | −0.8 | +1.2 | +0.07 |
| | Significance | | S | NS | S | | NS | NS | S |
| Fundus: | Treated eye | 14 | −1.4 | −0.2 | +0.05 | 14 | −0.7 | +0.1 | +0.09 |
| | Untreated eye | | −0.2 | +0.2 | 0.00 | | −0.4 | −0.9 | +0.02 |
| | Difference | | −1.2 | −0.4 | +0.05 | | −0.3 | +1.0 | +0.07 |
| | Significance | | S | NS | S | | NS | NS | S |

* Significant.
† Not significant.

outflow facility to 4% pilocarpine than subjects with heavily pigmented structures.

Similar results were obtained after the use of 2% epinephrine, except that insignificant changes were found in the initial tonographic tension irrespective of pigmentation (Table 2).

When the responsiveness of Negroes to 4% pilocarpine and 2% epinephrine was compared to that of Caucasians with all degrees of pigmentation, the Negro subjects appeared less responsive to these agents (Table 3).

## DISCUSSION

The results of these single-dose experiments indicate that persons with heavily pigmented skin, irides, trabecular meshwork; and fundi are less responsive to the pressure and outflow facility effects of 4% pilocarpine and 2% epinephrine than those with lightly pigmented structures.

Most of the subjects in the heavily pigmented categories were Negroes. A valid comparison between the responsiveness of Negroes versus darkly pigmented Caucasians could not be made because of the insufficient number of darkly pigmented Caucasians in each category.

A comparison was made between the lightly pigmented and medium pigmented Caucasian groups. There was no significant difference between the two in their response to the pilocarpine and epinephrine. This may be due to the lesser contrast in the quantity of pigmentation in the two groups. The

TABLE 3

AVERAGE CHANGE IN PRESSURE AND FACILITY OF OUTFLOW IN NORMAL CAUCASIAN AND NEGRO EYES TWO HOURS AFTER TREATMENT WITH 4% PILOCARPINE AND 2% EPINEPHRINE COMPARED WITH THE UNTREATED EYES

| Drug | | Caucasians | | | | Negroes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. Eyes | Δ Tap mm Hg | Δ $P_0$ mm Hg | ΔC μl/min/ mm Hg | No. Eyes | Δ Tap mm Hg | Δ $P_0$ mm Hg | ΔC μl/min/ mm Hg |
| 4% Pilocarpine: | Treated eye | 15 | −2.3 | −3.1 | +0.08 | 11 | −1.2 | −1.8 | +0.08 |
| | Untreated eye | | −1.2 | −1.3 | −0.02 | | −0.8 | −0.9 | +0.03 |
| | Difference | | −1.1 | −1.8 | +0.10 | | −0.4 | −0.9 | +0.05 |
| | Significance | | S* | S | S | | NS† | NS | NS |
| 2% Epinephrine: | Treated eye | 15 | −2.0 | −0.6 | +0.07 | 11 | −0.7 | +0.3 | +0.09 |
| | Untreated eye | | −0.7 | −0.6 | −0.05 | | −0.4 | -·0.8 | +0.04 |
| | Difference | | −1.3 | 0.0 | +0.12 | | −0.3 | +1.1 | +0.05 |
| | Significance | | S | NS | S | | NS | NS | NS |

* Significant.
† Not significant.

question of whether the degree of responsiveness is related to race or simply to the amount of pigmentation could not be determined.

A follow-up study will be made in which a group of Caucasians with irides as dark brown as possible will be compared to the lightly pigmented Caucasian group. This may still not give a conclusive answer since the subjective evaluation made in this study indicates that the quantity of pigment in the Negro iris is far greater than that found in the dark brown Caucasian iris.

## SUMMARY

Twenty-three subjects with normal eyes were evaluated as to the amount of pigment in their skin, irides, trabecular meshwork, and fundi. The tonometric and tonographic response of each eye to 4% pilocarpine and 2% epinephrine was made. The differences in the pre- and post-medication applanation pressures, opening tonographic pressures, and outflow facilities were calculated. The values obtained in the lightly and heavily pigmented treated eyes were compared to their untreated eyes.

It was found that the tonometric and tonographic response of darkly pigmented normal eyes to 4% pilocarpine and 2% epinephrine was less than the response of lightly pigmented eyes.

## ACKNOWLEDGMENT

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# SYSTEMIC VASODILATORS, INTRAOCULAR PRESSURE, AND CHAMBER DEPTH IN GLAUCOMA

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The present tests were made to evaluate the effects of the systemic vasodilator agents nicotinic acid, cyclandelate, and carbon dioxide on intraocular pressure in open-angle glaucoma, and to attempt in patients with abnormally narrow angles to induce angle-closure glaucoma by means of carbon dioxide, as previously unsuccessfully attempted with nitrate and nitrite vasodilators by Becker,[1] and by Whitworth and Grant.[2] Nicotinic acid was chosen for testing because it is a well-known vasodilator, and cyclandelate because of its current popularity. A 10% carbon dioxide-90% oxygen mixture was chosen for testing because this is reputed to be one of the most effective agents to induce dilation of vessels in the eye and in the brain, and might provide an indication of the maximum effect to be expected from any type of vasodilator agent that did not simultaneously cause severe changes in blood pressure.

Intraocular pressure was measured by applanation tonometry, using variously the Goldmann, Draeger, and Perkins optical instruments, with the patients in both sitting and prone positions, but always comparing measurements with the same tonometer and same position with and without test drug. When the effects of nicotinic acid and cyclandelate were being evaluated, pressure was measured hourly during five hours, with and without drugs, on separate days at the same times of day in order to take diurnal variations into account. Axial depth of the anterior chamber was similarly repeatedly evaluated with the standard Jaeger depth measuring attachment on the Haag-Streit 900 slit lamp with and without test medications.

When the effect of carbon dioxide inhalation was to be evaluated, a mixture of carbon dioxide 10% with oxygen 90% was delivered at a rate of 15 liters per minute to a face mask equipped with a rubber breathing bag and check valves to minimize variation or elevation of pressure within the mask. Intraocular pressure was measured in both eyes every one to two minutes with the patient in the supine position, using portable Draeger or Perkins applanation tonometers. The measurements were started 10 to 12 minutes before beginning inhalation of the carbon dioxide mixture, continued for eight to 10 minutes during inhalation, and for a variable period thereafter. Variations of axial depth of the anterior chambers were not measured during the tests with carbon dioxide because the time of exposure was short and was pre-empted by frequent applanation tonometry.

## Test results

Nicotinic acid in a single 100 mg oral dose was given to 14 patients. In 12 of these, chronic primary open-angle glaucoma was bilateral; in another patient, glaucoma was definite in only one eye, and in still another, the disease was borderline. Of these patients, 10 were receiving no antiglaucoma medication during the testing, but the other four were maintained under constant treatment with standard antiglaucoma medications (various combinations of miotics, epinephrine, and carbonic anhydrase inhibitors). In the absence of nicotinic acid, the tensions of all patients remained within the range of 20 to 35 mm Hg, most being close to 30 mm Hg. During the first two hours after administration of the nicotinic acid, most patients ex-

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perienced sensations attributable to cutaneous vasodilation. The axial depth of the anterior chambers measured hourly during four to five hours showed no change significantly different from the range of variation established in the absence of the test drug. Intraocular pressure measured hourly during the same period and compared with tension curves established in the absence of nicotinic acid at the same time of day showed no appreciable change in nine of the 14 patients. In the other five patients, the average level of the test curves for individual eyes differed from the curves without test medication by 1.5 to 3 mm Hg, but the test curves were no more often higher than lower. The extremes of transient differences between pressure curves for individual eyes with and without nicotinic acid ranged from 6 mm Hg briefly higher in one eye to 7 mm Hg briefly lower in another eye. The results are summarized in Table 1. Results with nicotinic acid in patients in the supine position were not appreciably different from those in patients who were sitting upright.

Cyclandelate in a single dose of 200 mg was given by mouth to 17 patients, of whom 14 had chronic primary open-angle glaucoma in both eyes, and two had what appeared to be the same type of glaucoma in only one eye, and one was considered an open-angle glaucoma suspect. Standard topical antiglaucoma medications were taken by five of these patients in the same manner before and during testing with cyclandelate; the other 12 were not under antiglaucoma treatment. During five hours after the dose of cyclandelate, no effects were noted by the patients, and during this time the axial depths of the anterior chambers did not change significantly, varying no more than ± 0.1 mm, the same as in the absence of cyclandelate.

TABLE 1

DIFFERENCE BETWEEN OCULAR TENSION CURVES WITH AND WITHOUT NICOTINIC ACID

| Mean Difference* (mm Hg) | No. Eyes |
|---|---|
| +3.0† | 1 |
| +2.5 | 1 |
| +1.5 | 1 |
| 0 | 21 |
| −1.0 | 1 |
| −1.5 | 1 |
| −2.5 | 1 |
| −3.0 | 1 |

* Mean of mean differences for all eyes = −0.036 mm Hg.

† A + indicates higher tension with nicotinic acid.

By inspecting the pairs of curves of hourly intraocular pressure measurements for each eye with and without cyclandelate we could discern no tendency for either a rise or a fall of pressure after cyclandelate. There appeared to be no distinguishing characteristics in the wanderings of the curves during the corresponding hours of the day with or without the drug. The same conclusions were indicated whether measurements were made with patients sitting or recumbent. During the five hours after administration of cyclandelate a fall of pressure occurred as frequently as a rise, and in all but one eye the changes in intraocular pressure during the five hours after administration of cyclandelate were within a range of ± 5 mm Hg of the starting pressure. The mean of the changes in intraocular pressure during the five hours after cyclandelate was a rise of 0.21 mm Hg. The one exceptional eye that had a change in pressure outside of the ± 5 mm Hg range had a rise of 9 mm Hg, but this corresponded almost exactly to the spontaneous rise of pressure in the same eye without cyclandelate on the control day, and appeared therefore not to be attributable to the medication.

The influence of cyclandelate on the intraocular pressure was further evaluated by determining in each of the 34 eyes of the 17 patients the difference between the pressures with and without the cyclandelate at hourly intervals for five hours following the administration of the drug. The mean difference for each eye with and without the drug was calculated by averaging the five hourly differences. The frequency distribution of these

TABLE 2

DIFFERENCE BETWEEN OCULAR TENSION CURVES WITH AND WITHOUT CYCLANDELATE

| Mean Difference (mm Hg) | No. Tests |
|---|---|
| +8* | 0 |
| +7 | 0 |
| +6 | 1 |
| +5 | 1 |
| +4 | 2 |
| +3 | 2 |
| +2 | 5 |
| 0(±1.5) | 21 |
| −2 | 3 |
| −3 | 1 |
| −4 | 0 |
| −5 | 0 |
| −6 | 1 |
| −7 | 0 |
| −8 | 1 |

* A + indicates higher tension with cylandelate.

mean differences, rounded to the nearest mm Hg is listed in Table 2. The mean of all the mean differences in intraocular pressure with and without cyclandelate indicated that during the five hours after administration of the test drug the intraocular pressure was 0.36 mm Hg higher with the cyclandelate than without. The initial premedication pressures on control days and drug test days ranged from 6 mm Hg higher to 7.8 mm Hg lower, but the mean difference was very small—0.13 mm Hg lower on the test days than on the control days. At each hour after the administration of cyclandelate the mean differences in the control and test pressure curves were as follows: end of first hour, +0.32 mm Hg difference; second hour, +0.47; third hour, −0.13; fourth hour, +0.58; fifth hour, +0.47 mm Hg.

We conclude from the observations on cyclandelate that a 200 mg oral dose has so little influence, if any, on intraocular pressure in glaucoma that it presents no appreciable danger to use in the presence of this disease.

Carbon dioxide, as a mixture of carbon dioxide and oxygen, was administered to four patients who had untreated chronic primary open-angle glaucoma in both eyes, and to five patients who had normal intraocular pressures but angles so narrow that gonioscopically it was difficult to ascertain that they were not closed. In four out of five of the latter group of patients, darkroom tests were negative and they had no known spontaneous elevations of pressure, but the fifth patient, whose angles looked almost totally closed, was known to have had spontaneous rises of tension to 30 and 32 mm Hg. In response to inhalation of carbon dioxide the intraocular pressure behaved essentially the same in the patients with open-angle glaucoma as in the patients with initially normal pressures but extremely narrow angles. Characteristically, the pressure rose during the first two minutes to an average peak 3.3 mm Hg above the start, then gradually subsided during five to six minutes toward the pre-inhalation level despite continued breathing of the carbon dioxide-oxygen mixture. The maximum transient rise was 8 mm Hg in one eye. When ordinary air was breathed again after eight to 10 minutes of inhalation of the carbon dioxide mixture, the intraocular pressure in all patients dropped transiently below the pre-inhalation level, usually 2 to 4 mm Hg below, but as much as 7 mm Hg in one patient. Then gradually, during 15 to 20 minutes of ordinary air breathing, the intraocular pressure came back up to the same level as before carbon dioxide inhalation. The carbon dioxide-oxygen mixture failed to provoke angle-closure glaucoma in any of the eyes.

## CONCLUSIONS

We believe that the literature has so far provided no valid evidence that vasodilator drugs such as those used in treatment of coronary or peripheral vascular disease have adverse effects on eyes with primary open-angle glaucoma, or on eyes that are anatomically predisposed to or subject to angle-closure glaucoma. References to literature on vasodilator drugs in relation to intraocular pressure are given in a review by Grant.[3] In

addition, Zahn[4] has reported that any rise of intraocular pressure after orally administered nitroglycerin or nicotinic acid was "insignificant," and Hayatsu and associates[5] have reported that cyclandelate given orally had no adverse effect on ocular pressure in normal or diseased human eyes, including glaucomatous eyes.

In the present study, tests of nicotinic acid and cyclandelate in patients with chronic open-angle glaucoma have shown no consistent influence on intraocular pressure, either good or bad, during four to five hours after single standard doses.

Our tests of 10% carbon dioxide inhalation have, however, shown this to cause a rise of intraocular pressure detectable within a minute or two and averaging 3.3 mm Hg, but as high as 8 mm Hg in one patient. This provides evidence that vasodilation, if sufficiently rapid and intense, can cause a transitory elevation of intraocular pressure. The time course of the pressure rise and subsidence associated with inhalation of carbon dioxide is consistent with a rapid but small increase in blood volume and with the expected effect of automatic compensatory expulsion of an equivalent volume of aqueous humor from the eye. When the inhalation of carbon dioxide is terminated and the vasodilating influence is removed, the volume of the intraocular vessels apparently promptly decreases, as indicated by the drop in pressure immediately after stopping the inhalation. A gradual compensatory reaccumulation of the small volume of aqueous that was expelled earlier then brings the intraocular pressure back to the original steady state.

These observations with carbon dioxide seem consistent with those on the slower and longer-acting vasodilator drugs, pointing to the capability of the human eye, even when afflicted with chronic open-angle glaucoma, to compensate rapidly for finite changes in intraocular vascular volume. These observations suggest that the maximum change in intraocular pressure to be expected from vasodilator drugs that do not greatly alter blood pressure is of the order of a few mm Hg, and may be expected to be transitory. If vasodilator drugs had an influence on either facility or pseudo-facility of aqueous outflow, or on orbital or episcleral venous pressure, they presumably could exert a sustained influence on intraocular pressure different from the transitory influence of finite change in intraocular blood volume. A mechanism for interfering with aqueous outflow has not yet been demonstrated in connection with systemically administered vasodilator drugs, although in explaining the action of vasodilators injected subconjunctivally, such a mechanism may need to be considered.

Failure to provoke angle-closure glaucoma by means of carbon dioxide-oxygen mixture in the five patients with initially normal intraocular pressures but extremely narrow angles was disappointing from the standpoint of search for better provocative tests for angle-closure glaucoma, but it was consistent with the fact that there is an absence of adequately documented reports that establish a relationship between vasodilator drugs and precipitation of acute angle-closure glaucoma. Probably the volume of expansion of intraocular vessels induced by vasodilator drugs is generally too small to induce significant forward bulging of peripheral iris. Neither nicotinic acid nor cyclandelate caused appreciable forward movement of the lens. The angle may have to be extremely critically narrowed before drug-induced change in volume of blood vessels posterior to the lens-iris diaphragm is likely to complete the closure.

It is noteworthy in this connection that attempts by Segal and associates[6] to induce angle-closure glaucoma by utilizing pressure breathing have been unsuccessful, although it has been demonstrated by Pilz and Comberg[7] that this procedure raises intraocular venous pressure and volume.

It appears that the literature and the present clinical testing have provided no valid grounds for withholding coronary and peripheral vasodilator drugs from patients with

chronic primary open-angle glaucoma. Also it appears, contrary to old ideas, that precipitation of angle-closure glaucoma by systemic vasodilator drugs must be a rare occurrence, if indeed it does occur. Further testing would be worthwhile in subjects who have well-established intermittent spontaneous episodes of angle-closure glaucoma.

## Summary

Nicotinic acid (100 mg) was administered to 14 patients and cyclandelate (200 mg) to 17 patients, most of whom had untreated open-angle glaucoma. There was no appreciable influence on anterior chamber depth and so little influence on intraocular pressure that it was concluded that use of these medications in the presence of glaucoma should present no significant danger. Inhalation of 10% carbon dioxide-90% oxygen mixture by four patients with open-angle glaucoma and by five patients with normal pressure but extremely narrow angles caused the intraocular pressure to rise a few mm Hg within two minutes, but this was transient and subsided within five to six minutes. It did not induce angle-closure glaucoma. These tests, and a comprehensive search for published clinical evidence, indicate that if there is a risk of inducing angle-closure glaucoma or of aggravating open-angle glaucoma by systemic vasodilators, it has not yet been demonstrated and the risk must be extremely small.

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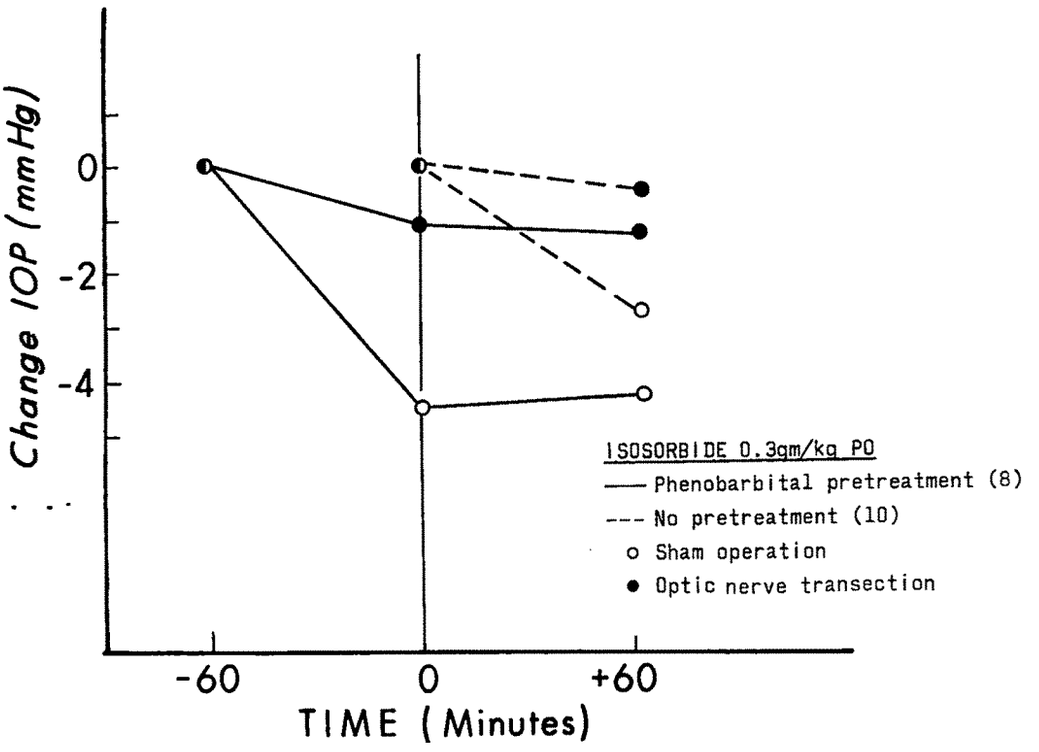



Fig. 2 (Podos, Krupin, and Becker). Influence of pretreatment with intravenous phenobarbital, 52 mg/kg, on the change in intraocular pressure of rabbits with unilateral optic nerve transection after oral administration of isosorbide, 0.3 g/kg. (n = number of animals.)

the decrease of intraocular pressure after phenobarbital, 13 mg/kg, and isosorbide, 0.3 g/kg, remained significantly ($p < 0.001$, $p < 0.01$) less in eyes with transected optic nerves than in their mates with intact optic nerves (Table 2).

### Intravitreal experiments

The half lives of $^{131}$I-iodohippurate injected into the vitreous of three rabbits did not differ between the eyes subjected to sham operation and optic nerve transection (Table 3). The concentration of $^{131}$I-iodohippurate in the anterior chamber aqueous humor remained negligible in all eyes tested.

## Comment

A number of possible explanations exist for the lesser intraocular pressure response to certain agents of an eye that has had its optic nerve and sheath transected. One can suspect that other orbital structures are being damaged. However, the same procedure with exception of actual transection is carried out on the control fellow optic nerve of rabbits[1] and intracranial transection is performed in the monkey.[2] In both, no visible change of retinal blood supply occurs.

A direct effect on the eye is certainly feasible. Alterations of permeability, either vascular or bulk via the cut optic nerve, or of some transport mechanism, anterior or posterior, are possible explanations. However, many pieces of information do not fit this hypothesis. Baseline intraocular pressure and outflow facilities are consistently symmetrical in animal eyes with transected and intact optic nerves. Differences in these parameters might be expected if one eye is "leakier" than the other. In addition to the

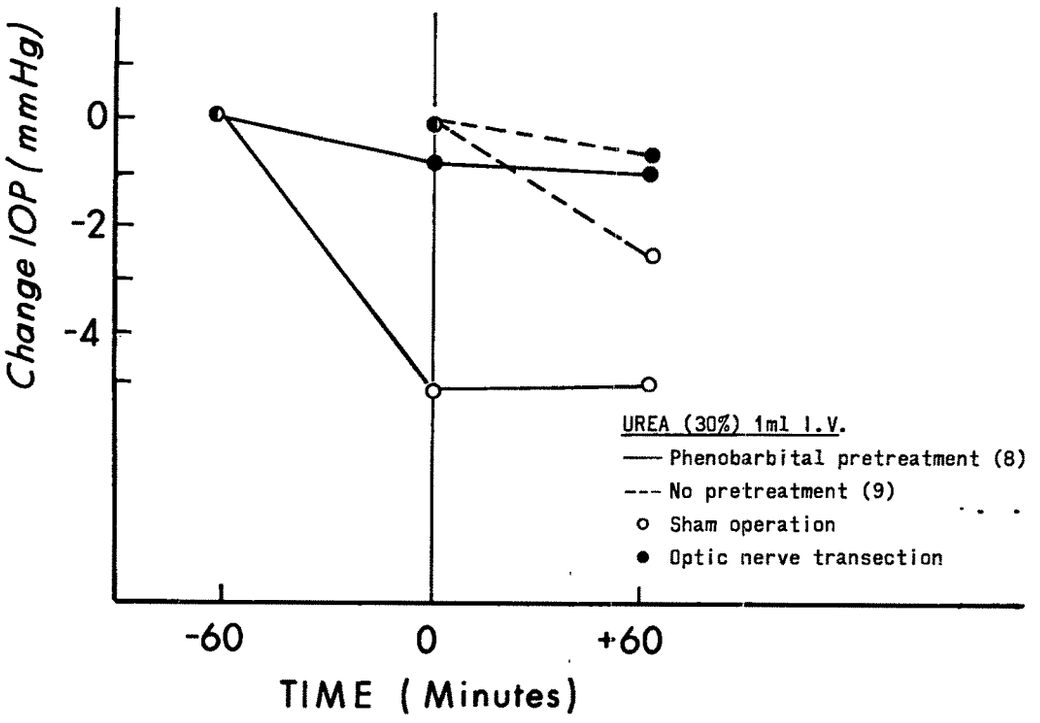



Fig. 3 (Podos, Krupin, and Becker). Influence of pretreatment with intravenous phenobarbital, 52 mg/kg, on the change in intraocular pressure of rabbits with unilateral optic nerve transection after small single bolus intravenous administration of urea, 1 ml per animal. (n = number of animals.)

osmotic agents, barbiturates produce a differential response.[2,4] Permeability changes are not expected to affect the action of the barbiturates. Furthermore, large doses of hyperosmotic or hypo-osmotic agents do not produce a differential intraocular pressure response in these animals.[1] The effective agents given in excess appear to overload the system or act in different fashion. Acetazolamide or topical agents also produce bilateral symmetrical changes.[3] Thus, certain drugs reduce intraocular pressure equally in both eyes of this animal preparation. After administration of isosorbide in an amount that produces less diminution of intraocular pressure in the eye with a cut optic nerve, vitreous and aqueous osmolarity is the same in both eyes of rabbits.[1] However, this may be too gross a test to detect the small potential differences of permeability necessary to account for intraocular pressure differences.[8] An ocular transport system secretes intravitreal organic acids out of the eye.[7] The half-life of $^{131}$I-labeled iodohippurate is not significantly different in the vitreous of eyes with and without intact optic nerves (Table 3) and $^{131}$I-iodohippurate does not accumulate in anterior chamber aqueous. This suggests that optic nerve transection does not alter the posterior pump for iodohippurate.

Therefore, a reasonable working hypothesis involves a central nervous system pathway responsive to some agents and not to others. One can postulate a dual mechanism with separate mediators for elevating and lowering intraocular pressure. Interruption of the tonus of both paths results in no change of baseline intraocular pressure. Stimulation or inhibition of one pathway would lead to the observed differential responses of eyes with transected and eyes with intact optic nerves.

If the same receptor is responsible for all of the intraocular pressure lowering re-

TABLE 2

ALTERATIONS OF INTRAOCULAR PRESSURE INDUCED IN RABBITS WITH UNILATERAL OPTIC NERVE TRANSECTION PRETREATED WITH PHENTOLAMINE

| Drug | Dose | No. Animals | Optic Nerve Transected (Mean ±SEM) | | | Sham-Operation (Mean ±SEM) | | |
|---|---|---|---|---|---|---|---|---|
| | | | $P_0$* | $P_1$ | $\Delta P$ | $P_0$ | $P_1$ | $\Delta P$ |
| Isosorbide (po) | 0.5 g/kg | 6 | 12.3 ±0.4 | 10.6 ±1.0 | −1.7 ±0.8 | 12.5 ±1.3 | 9.4 ±1.1 | −3.1 ±0.7 |
| | 0.3 g/kg† | 6 | 10.9 ±0.5 | 11.0 ±0.5 | +0.1 ±0.2 | 11.2 ±0.6 | 8.8 ±0.5 | −2.4 ±0.7 |
| Water (po) | 37.5 ml/kg | 7 | 14.2 ±0.9 | 18.2 ±0.8 | +4.0 ±0.7 | 13.8 ±0.7 | 17.8 ±0.8 | +4.0 ±0.5 |
| | 25 ml/kg | 6 | 12.8 ±0.3 | 13.2 ±0.4 | +0.3 ±0.4 | 13.3 ±0.5 | 13.9 ±0.7 | +0.6 ±0.7 |
| Phenobarbital (IV) | 13 mg/kg‡ | 7 | 13.6 ±1.1 | 10.9 ±0.7 | −2.7 ±1.2 | 14.0 ±0.9 | 9.0 ±0.6 | −5.0 ±1.0 |

* $P_0$ is initial intraocular pressure in mm Hg, $P_1$ is intraocular pressure one hour after isosorbide and phenobarbital or one-half hour after water, $\Delta P$ is $P_1 - P_0$.

† Significant difference between change of intraocular pressure of transected vs sham-operated eye, $p < 0.01$.

‡ Significant difference between change of intraocular pressure of transected vs sham-operated eyes, $p < 0.001$.

ceptors,[9] receptive to small injections of hypertonic solutions.[10] Electric stimulation of hypothalamic nuclei alters intraocular pressure.[11] Barbiturates have depressant effects on the hypothalamus.[12] Similarly, the pathway from the hypothalamus to the eye is obscure, but efferent fibers in the optic nerve are described[13,14] and traced from the anterior hypothalamus.[15] Histopathologic degeneration studies and hypothalamic stereotactic stimulation experiments in animals with unilaterally transected optic nerves are in progress.

TABLE 3

HALF-LIFE OF INTRAVITREAL $^{131}$I-LABELED IODOHIPPURATE IN THREE RABBITS WITH UNILATERAL OPTIC NERVE TRANSECTION
(Half-life in minutes)

| Optic Nerve Transected | Sham Operation |
|---|---|
| 220 | 210 |
| 230 | 250 |
| 210 | 220 |
| Mean 220 | 227 |
| SEM ±5 | ±10 |

It is certainly not yet clear how the postulated pathway affects aqueous humor dynamics. Hypothalamic stimuli do affect sympathetic nerve activity in a number of organs.[16] Histochemical staining of adrenergic and cholinergic nerves is found to be weak but present in the optic nerve and strong in adjacent ciliary nerves,[17] ciliary body, and filtration area.[18] Species variation is noted. Moreover, cholinergic centrifugal nerves are demonstrated in the optic nerve of the rat.[19]

In the present study, chemical adrenergic or cholinergic blockade of the response of the rabbit eye subjected to a sham operation, to low-dose osmotic agent, or phenobarbital occurs so that the intraocular pressure differential between eyes with and without intact optic nerves is no longer apparent. Parasympathetic paralysis with systemically administered atropine does not alter the pressure elevating response to water ingestion in the sham-operated eye as compared to the

eye with a transected optic nerve. However, the decrease of intraocular pressure induced by low-dose isosorbide and phenobarbital is reduced in the intact eye so that both eyes now respond equally after pretreatment with atropine (Table 1). The small decrease after isosorbide or phenobarbital in the sham-operated eyes of atropinized rabbits compares favorably to prior results in nonatropinized eyes with transected optic nerves.[1,4] In experiments with topical application of atropine, this blocking effect is not found.[8]

Utilization of adrenergic blockade is complicated by the fact that the sympathetic system appears to have two types of adrenotropic receptors.[20] In the eye, for instance, the transient effect of norepinephrine released by superior cervical ganglionectomy on outflow facility is greatly reduced by systemically administered phentolamine (an α-adrenergic blocking agent,)[21] but not by propranolol (a β-adrenergic blocking agent).[22] Less is known about the presence of these two types of receptors in the aqueous secretory apparatus. Intravenous phentolamine decreases intraocular pressure equally in eyes with and without intact optic nerves.[8] Systemic pretreatment with phentolamine has little or no effect on the greater decrease of intraocular pressure of the eye with an intact optic nerve after isosorbide or phenobarbital as compared to the fellow eye with a cut optic nerve. However, no significant difference occurs between the elevation of intraocular pressure of the transected and sham-operated groups induced by water ingestion in animals so pretreated (Table 2). Superior cervical ganglionectomy seems to provide equivocal data, somewhat similar to that with phentolamine but not statistically significant.[8]

Thus, it is tempting to speculate that the end-organ response in eyes with intact optic nerves for the agents that lower intraocular pressure differentially is mediated through a cholinergic system. The intraocular pressure elevating effect of water appears to be mediated through an α-adrenergic mechanism. Optic nerve transection obliterates both types of responses. The specific effects on inflow and outflow, by either conventional or unconventional routes, are not completely understood, but available information favors effects on secretion of aqueous humor. The decrease of outflow facility induced by water is symmetrical in the two eyes of our animal preparations.[1] Isosorbide does not alter outflow facility.[23] There is evidence that barbiturates decrease aqueous humor secretion and do so more in rabbit eyes with intact optic nerves than in their fellow eyes with transected optic nerves.[4]

## Summary

Mechanisms were investigated for the lesser intraocular pressure response to barbiturates, hyperosmotic and hypo-osmotic agents of rabbit eyes with transected optic nerves as compared to their sham-operated fellow eyes. Phenobarbital pretreatment prevented the subsequent diminution of intraocular pressure in eyes with intact optic nerves after administration of small doses of oral isosorbide or intravenous urea, but did not alter the intraocular pressure elevation after water ingestion. The greater intraocular pressure fall in eyes with intact optic nerves after isosorbide or phenobarbital did not occur in atropinized rabbits but the differential rise in intraocular pressure after water persisted. In rabbits pretreated with phentalomine, the greater diminution of intraocular pressure in sham-operated eyes after isosorbide or phenobarbital remained, while the elevation of intraocular pressure after water was similar in eyes with and without transected optic nerves. The half-life of intravitreal $^{131}$I-labeled iodohippurate sodium was similar in eyes after transection of the optic nerve and after sham operation, and in neither group did the isotope accumulate in anterior chamber aqueous.

### Acknowledgments

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# CORNEAL HEMOCHROMATOSIS

## A Unique Type of Corneal Dystrophy Involving the Anterior Stroma and both Limiting Membranes

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The variety of degenerative processes of the cornea encountered in clinical practice seems to have no end. The changes seen in the patient herein reported did not conform either biomicroscopically or pathologically to those recorded in any of the types described in the literature.

### Case report

A 41-year-old man of Italian descent, who had always had decreased visual acuity sufficiently low to exempt him from military service, suffered further visual disability over approximately six months. At no time did he have pain, discomfort, or other subjective disturbances. He was alert, well developed and in good health. His one sibling, a sister aged 38 years, was normal, as were both parents. There was no consanguinity.

When the patient was first seen on June 14, 1967, uncorrected visual acuity was 20/200- in the right eye and 4/100- in the left. The eyes showed no congestion; no blepharospasm or lacrimation were present. Upon applanation, intraocular pressure was 18 mm Hg in both eyes.

External examination disclosed bilaterally a fine, diffuse, grayfish cloudiness of the entire cornea (Fig. 1). Corneal sensitivity was undisturbed.

*Biomicroscopic study*—Corneal luster was preserved and the epithelium appeared to be normal. The opacity, of uniform density throughout, was confined to the anterior third of the stroma. It seemed to be composed of a multitude of minute refringent dots resembling lipid droplets. No changes were seen in the posterior two-thirds of the stroma. Descemet's membrane appeared to be somewhat thickened and slightly irregular. There was no neovascularization. The corneal thickness, measured with the Haag-Streit pachometer, was normal.

The iris, lens and internal media were normal.

*Ophthalmoscopic study*—Examination under wide dilation of the pupils failed to reveal any gross abnormality. Although the corneal opacity obscured fundus details, the disks and maculas seemed to be normal.

*Physical examination*—Full medical examination excluded the presence of any systemic disorder. In particular, there was no hepatomegaly, splenomegaly, or diabetes, and no abnormal pigmentation of the skin. The patient was impotent. Repeated urinalyses, blood cell counts, blood sugar determinations and x-ray studies of the skull and chest were all negative. Total protein plasma content was 6.6 g/100 ml and the albumin-globulin ratio was normal, as were also the serum iron level estimated by the method of Barkan (136 μg/ml) and the glucose tolerance test. The liver function tests were normal: serum bilirubin was 0.70 mg %, the thymol turbidity test 6.1 units and the cephalin flocculation test ++ (48 hrs).

*Treatment*—On October 5, 1967, a 7-mm penetrating keratoplasty was performed on the left eye under local anesthesia. Fresh donor material and 16 appositional 7-0 black silk sutures were used. At the end of the procedure, air was injected into the anterior chamber. Sutures were removed on the 31st day, and the eye was left unpatched 48 hours later. The postoperative course was uneventful and the graft remained clear. On September 11, 1968, refraction of the left eye was −3.00 sph⊃ −2.25 cyl ax 25°. Although fully corrected vision was only 20/60, a clear view of the fundus, which was normal, could now be obtained.

Examination of the right eye at this time showed that its condition had worsened. The corneal opacity was more dense. Vision was now reduced to 4/200 and visualization of the fundus was no longer possible. Accordingly, on November 16, 1968, a 7-mm full-thickness corneal transplantation was performed on the right eye. Eight interrupted virgin silk sutures and a running monofilament Perlon suture were used, and the anterior chamber filled with air. The postoperative course was uneventful. The direct sutures were removed on the 14th day but the running suture was left in place for 60 days.

When the patient was last seen, on July 28, 1969, vision in the right eye was 20/60 with +4.50 sph⊃ −4 cyl ax 10°. The graft was clear. The fundus appeared to be normal and no explanation for the diminished visual acuity could be found. The condition of the left eye was unchanged.

### Pathology

The specimens taken from the recipient eyes were fixed in formalin and embedded in paraffin. In addition to the routine stains, a number of differential staining techniques were used.

The sections colored with hematoxylin-eo-

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Fig. 3. (Urrets-Zavalía and Katz). Broad gap (arrow) in Bowman's membrane, where the superficial stromal layers seem to be continuous with the newly formed plaques underlying the basement membrane. This dehiscence should not be confused with the numerous pores which are normally present in Bowman's membrane (hematoxylin-eosin, ×400).

sin showed irregularities in the underlying stratum which caused the epithelium to vary greatly in thickness (Fig. 2). The normal arrangement of cells was disrupted and there was slight edema with bulla formation. The epithelium had a tendency to become detached in places where a delicate, avascular fibrous tissue, similar to that of the substantia propria, separated it from Bowman's membrane. This was uneven and frayed; it showed some gaps where the superficial stromal layers appeared to be continuous with the newly formed plaques beneath the epithelium (Fig. 3).

The posterior two-thirds of the stroma was unaltered. In the anterior third, however, was an accumulation of amorphous granules which stained a dark violet; at no place between the epithelium and Bowman's membrane did the stain demonstrate this material. Although the deposits caused separation of the corneal lamellae, these showed only minor and nonspecific degenerative changes. A strongly basophilic membrane of a barely discernible fibrillar nature replaced Descemet's membrane; it was about twice the thickness of Bowman's membrane. The endothelium appeared to be extremely thin and was absent in some places; its irregularly distributed cells exhibited pleomorphism and severe pyknotic changes.

With Masson's trichrome the microdeposits in the stroma took on a deep purple color (Fig. 4). It is interesting that with this stain, the posterior membrane appeared to be situated in front of what remained of Descemet's membrane. It was composed of two layers, each with a different tinctorial affinity: the anterior layer was pink; the posterior one blue. A faint transverse striation could be seen in both layers (Fig. 5). There were some stromal changes adjacent to that membrane.

The granules appeared red, as did the nuclei, with Mallory's stain (Fig. 6).

The toluidine blue stain revealed no metachromasia (Fig. 7). Both the interlamellar deposits and the posterior membrane stained a brilliant blue.

The alcian blue and the periodic acid-Schiff (PAS) reactions failed to stain the nodules (Fig. 8). However, PAS showed that the posterior membrane consisted indeed of two distinct layers: an anterior one which stained magenta and a faint blue posterior one (Fig. 9). Both layers stained more intensely than the parenchyma.

The Perls test, used with an erythrosin counterstain, gave a green color to the stromal accumulations, strongly suggesting that hemosiderin—or at least iron—was present (Prussian blue reaction). The membrane seen



Fig. 11 (Urrets-Zavalía and Katz). In the completely incinerated specimen, iron oxide imparts to the ash a bright orange color (areas marked with black rings). Oblique illumination on dark field (×640).

posteriorly exhibited the curious doubling already noted, the anterior half being a pale green, the posterior half pink (Fig. 10).

The Johnson method for iron (microincineration) was also positive: When examined with oblique illumination on a dark field, the completely incinerated specimen showed many dark red deposits in the anterior stroma and an orange discoloration of the anterior half of the membrane (Fig. 11). Direct observation of the Prussian blue reaction on ash revealed that iron oxide was present.

The Feulgen test for nucleic acid was strongly positive, the interlamellar material staining a deep pink (Fig. 12); it was negative at the level of the posterior membrane, which stained a very light pink, as did the stroma. The purpurin reaction for calcium was negative; the entire cornea, including the nodules and Descemet's membrane, assumed a uniform coloration when counterstained with methanile yellow (Fig. 13).

## Comment

Franceschetti and Babel[1,2] first discussed the histopathologic differentation of the three classic corneal dystrophies involving the corneal stroma—granular, lattice, and macular. Jones and Zimmerman[3,4] and Smith and Zimmerman[5] later detailed the differences more clearly. They resorted to certain histochemical reactions in addition to the standard staining techniques and their findings are the yardstick for appraisal of any observation that is deemed unusual. We have used these criteria to assess the observation reported above.

In the granular, lattice, and macular corneal dystrophies, there is in the stroma a characteristic accumulation of an anhistous material, which is more or less eosinophilic and stains pale gray or pink with hematoxylin-eosin. This is in marked contrast to the results obtained in the case described, where the specific lesions were strongly basophilic and stained violet, being almost black with Masson's trichrome. With this reaction, the typical lesions of the granular and macular degenerations turn red, those of lattice degeneration a faint blue. The PAS reaction was negative in our case, as it is in granular dystrophy, revealing absence of mucopolysaccharides in the deposits. On the other hand, in the lattice and macular degenerations the lesions usually color a dark magenta with PAS. The deposits in the present case did not stain with Alcian blue, which makes the lesions in granular dystrophy turn pink, those in lattice dystrophy pinkish-red, and, owing to the presence of an acid mucopolysaccharide, those in macular dystrophy a deep blue.

But not only in its singular staining properties did the homogeneous material in the case being discussed differ from that existing in the more familiar forms. In these more familiar forms, it seems to result from the destruction and subsequent transformation of

the substantia propria, whereas in the case under discussion it was more in the nature of an inclusion between the fibers themselves. Moreover, the abnormalities we found in Descemet's membrane deserve special consideration as there is no previous report of a dystrophy in which this membrane exhibited a greater thickness and a striated appearance. In primary Fuchs' dystrophy, an additional laminated membrane overlying the *posterior* surface of Descemet's membrane, with excrescences between the two layers, has been reported as a rare finding by Chi, Teng, and Katzin.[6] This new membrane differed in its tinctorial properties from that seen in our case. Besides, it was covered with endothelium, which had abnormally large, thin, elongated nuclei, and contained fine granules of pigment.

If, in addition, one notes that the lesions in the patient under consideration differed clinically from those seen in the hereditary dystrophies studied by Bücklers,[7] it should be concluded that the condition in this case represents a separate morbid entity.

Franceschetti and Babel[8,9] mentioned a congenital corneal dystrophy in which the pathologic process invaded the whole cornea and showed little or no tendency to progress. It was characterized by a diffuse cloudiness and, in this one respect, resembled the picture observed by us. There the analogy ceases, for Franceschetti and Babel found the stromal lamellae ill-defined, dissociated into a mass of fine fibrils and drowned in a basophilic, edematous material. The basophilic granules they saw in the anterior layers of the stroma were small and few in number, and appeared to be attached to the stromal cells; they turned orange with the Mallory stain, which, in our case, dyed the granules red. The only other similar case in which a pathologic examination was made is that of Offret reported by Etienne.[10] In this case, the basophilic granules were more numerous and appeared in the interlamellar spaces. The lamellae were indistinct and poorly limited. A fine acidophilic intralamellar dust was also seen.

From the viewpoint of their staining properties, the stromal accumulations of granular dystrophy may be characterized as areas of hyaline degeneration, those of macular dystrophy as areas of mucoid degeneration, and those of lattice dystrophy as areas of amyloid degeneration.[5] Although the nature of the stromal inclusions found in the present case is not clear, the results with the Masson and Mallory stains, as well as the Feulgen reaction, seem to indicate the presence of nucleic acid. The Perls test and the microincineration test revealed that both the inclusions and the anterior layer of Descemet's membrane contained a ferrous compound.

This latter fact suggests that one could be dealing with an iron storage disturbance such as hemochromatosis (bronze diabetes, pigmentary cirrhosis), a rare condition which has been known to involve the eye occasionally and which results from an inborn error of the metabolism wherein excessive deposits of iron are laid down throughout the body in the form of brown granules. The accretion of iron is gradual, so that the symptoms do not usually appear until mid-adult life[11] (90% of the patients are over 35 years of age). It appears predominantly in the male (90%), the obvious explanation for this sex disparity being the ability of the female to unload considerable amounts of iron through menstruation, pregnancy and lactation[12]; thus, in women the disease is relatively more frequent after the menopause.[13]

It has not been demonstrated that huge accumulation of iron in the tissues will bring about by itself the pathologic changes and clinical manifestations of this morbid process. It seems more reasonable to consider that iron, which is not converted to the proper kind of ferric hydroxide, may cause cell destruction with consequent fibrosis by precipitating proteins indiscriminately, or perhaps by inactivating one or more specific enzymes.[14-16]

The tetrad of hepatomegaly with eventual liver insufficiency, slowly progressive diabetes mellitus, cardiac failure and a slate-

gray pigmentation of the skin is characteristic. A nontender, firm spleen is palpated in about one-half of the patients. Loss of hair, palmar erythema, testicular atrophy, and particularly loss of libido are often seen.[12] Elevation of the plasma iron concentration and of the iron-binding capacity are considered the most valuable presumptive diagnostic signs in hemochromatosis. Needle biopsy of the liver—which is highly demonstrative when the specimen contains an excess of hemosiderin—should be undertaken only when the former tests are positive.

While hemochromatosis is usually encountered sporadically, there is adequate evidence to indicate that it may occur as a familial disorder. Debré and co-workers[17] and Finch and Finch[12] point out that among the relatives of patients with the overt disease about 20% have elevated serum iron levels. The disorder is probably the result of an autosomal genetic defect of incomplete penetrance or variable expressivity, or both, which is transmitted as a Mendelian dominant.[18] Davidson[19] believes that it is probably transmitted as an autosomal recessive trait, whereas Powell[20] maintains that if an intermediate form of inheritance exists, there is as yet no clear distinction between the heterozygous and early homozygous states.

Idiopathic hemochromatosis must be distinguished from other iron storage diseases such as dietary and transfusion hemochromatosis, which are obviously the result of environmental factors. It should be noted that there is a definite association of alcoholism and Laennec's cirrhosis with hemochromatosis. Although the implications of this are not entirely clear,[12] the findings of Powell[20] support the notion that the idiopathic hemochromatosis and alcoholic cirrhosis are separate entities.

In its primary form, the condition is generally visualized as an enterogenous process, connected with the absorption of abnormally large amounts of iron in the absence of excessive intake. It has been shown to result from an intrinsic defect dependent upon an enhanced ability of the mucosal cells to let iron move from the duodenal tract into the blood stream.

In a review of the literature since 1930, Hudson[21] found very few references to the ocular changes, which for the most part are similar to those of diabetes such as retinal and conjunctival microaneurysms. A picture of early diabetic retinopathy was also observed by Galton.[22] Maddox[23] described in four cases a grayish-blue discoloration of the retina. The pigment deposition was of a diffuse and uniform character, but was especially concentrated around some or all of the disk margin. The pigment itself was not the common black color seen in the dark-skinned

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Figs. 1, 2, 4, 5, and 6 (Urrets-Zavalía and Katz). Figure 1 (top) : Right eye of 41-year-old man with diffuse, grayish cloudiness of entire cornea. The corneal luster is preserved. Figure 2 (center left) : Cross section of excised cornea showing marked irregularity in epithelium thickness with slight intracellular edema and superficial bulla formation. A thin layer of fibrous tissue separates the epithelial basement membrane from Bowman's membrane. An accumulation of dark violet staining granules may be seen in the substantia propria. A thick, strongly basophilic membrane replaces Descemet's membrane; it shows a faint striation in its anterior half. Endothelium is almost entirely absent (hematoxylin and eosin, ×100). Figure 4 (bottom left) : With Masson's trichrome, the stromal deposits take on a deep purple color. The connective tissue located under the epithelium is more cellular than the stroma. The membrane which exists on the posterior surface appears to be composed of two distinct layers (×100). Figure 5 (center right) : Posterior margin of field shown in Figure 4. Posterior membrane composed of two layers with different tinctorial affinities is situated in front of Descemet's membrane. The latter is reduced to barely discernible fragments. The endothelium is absent. Note stromal changes adjacent to posterior membrane (Masson's trichrome, ×400). Figure 6 (bottom right) : The specific stromal lesions color a vivid red with Mallory's stain. The corneal lamellae show more advanced changes than with hematoxylin-eosin (×400).

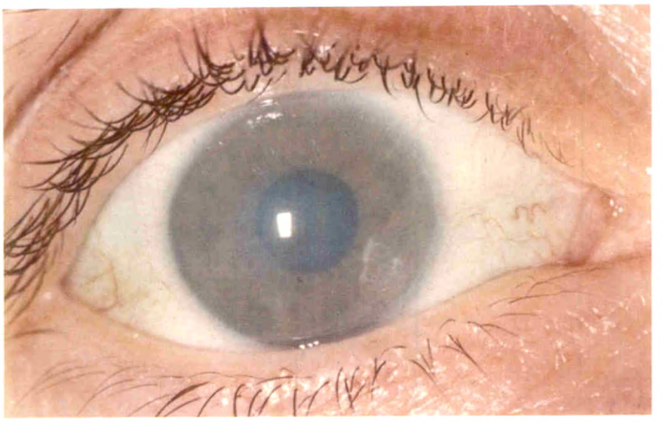


Fig. 1

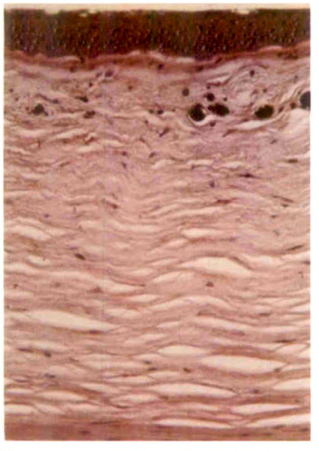


Fig. 2

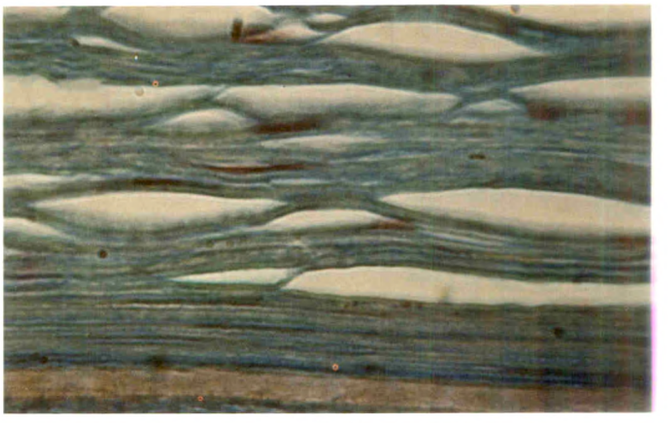


Fig. 5

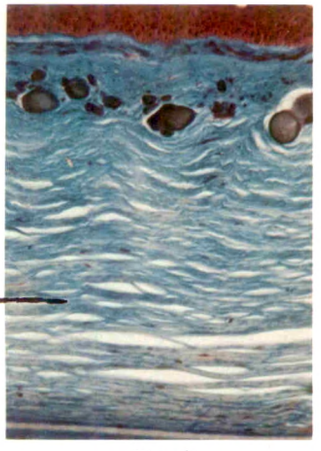


Fig. 4

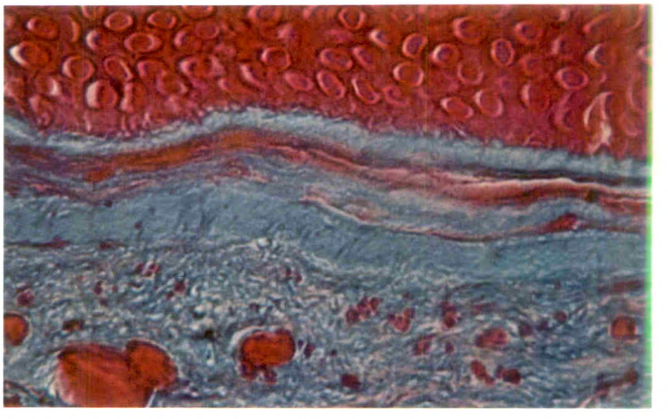


Fig. 6

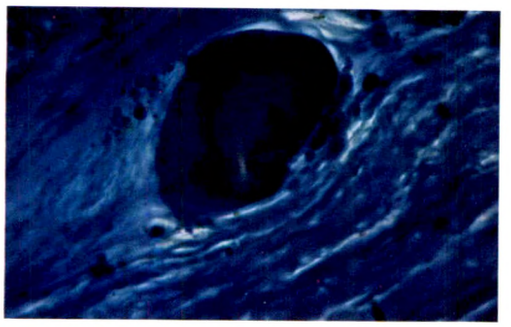


Fig. 7



Fig. 9



Fig. 8

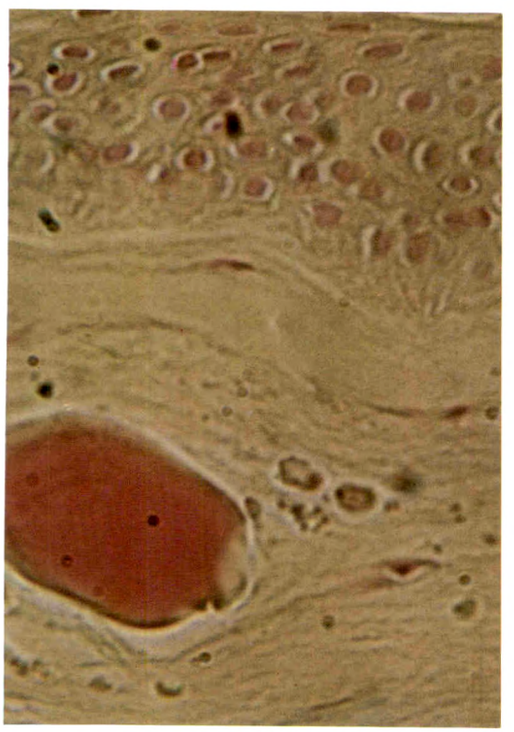


Fig. 12

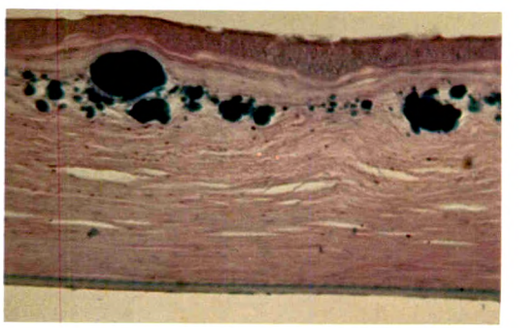


Fig. 10

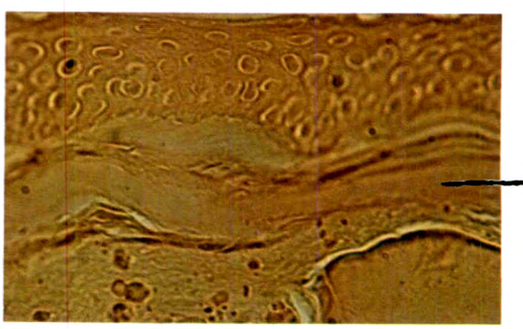


Fig. 13

TABLE 1

IRON CONTENT OF THE CORNEA[25]

| | Wet Tissue (μg/100 g) | | | Dry Tissue (μg/100 g) | | |
|---|---|---|---|---|---|---|
| | Minimum | Maximum | Average | Minimum | Maximum | Average |
| Whole cornea | 208 | 296 | 257* | 1000 | 1380 | 1160 |
| Stroma | 166 | 220 | 197 | 720 | 1000 | 890 |
| Epithelium | 552 | 680 | 616 | 2200 | 2720 | 2460 |

* Oksala's[24] figure for the overall iron content of the cornea is of 500 μg/100 g of the wet weight.

races but a deep slaty color through which the retina appeared as a kind of ochre background. To the best of our knowledge no corneal changes due to hemochromatosis have ever been detected.

In the propositus, nothing seemed to warrant a diagnosis of hemochromatosis, either primary or secondary. There was no demonstrable dysfunction or enlargement of the liver, which is the first organ to be affected, no diabetes or prediabetes, no pigmentation of the skin, and no excess iron in the serum. The corneas, nevertheless, were laden with iron, which was attached to a nucleoprotein.

Under normal conditions, iron is present in the cornea only as a trace element,[24] the average content being lower in the stroma than in the epithelium. Table 1, which is based on the determinations made by Tauber and Krause[25] in the eyes from freshly slaughtered cattle, gives the relative proportions of this metal in the cornea. In the case of the so-called Hudson-Stahli line, the Stocker line, and the Fleisher ring seen in keratoconus, there is a demonstrable focal deposition of intracytoplasmic iron in the corneal epithelium, although in minute quantities.[26]

Why the corneas in our patient should have such large stores of an iron protein in the stroma is a matter of speculation. The simplest view should be that this resulted from a purely local disturbance akin to that which leads to the appearance of a nonsystemic amyloidosis in the case of lattice dystrophy.[27-30] It ought then to be considered a variety of hemochromatosis restricted to the cornea wherein the deposition of iron in the form of clusters of a probably non-heme compound produces a degradation of collagen with degeneration of the fibroblasts. Alternatively, it might be that the insoluble protein in the stromal nodules picks up iron on a selective basis. It must be made clear at this point that by using the term "hemochromatosis" we are not postulating a connection as to the origin between the corneal deposits and the systemic affliction, or even the blood pigment. We seek only to provide the condition with a label which immediately brings to mind the idea of an accumulation in the tissues of an abnormal iron protein.

Figs. 7-10, 12, and 13 (Urrets-Zavalía and Katz). Figure 7 (top left): The corneal accumulations take on the same color as the surrounding stroma when treated with a metachromatic stain (toluidine blue, ×400). Figure 8 (top right): The stromal deposits do not stain with PAS-alcian blue (×400). Figure 9 (center left): Doubling and faint striation of posterior membrane (PAS, ×400). Figure 10 (center right): Hemosiderin present in stromal granules and anterior half of posterior membrane (Perl's test with erythrosine counterstain, ×60). Figure 12 (bottom left): Interlamellar deposits contain nucleic acid (Feulgen's test, ×400). Figure 13 (bottom right): No calcium is present in stromal granules (purpurin reaction with methanile yellow counterstain, ×400).

For the time being, one can only describe the peculiar changes in Descemet's membrane, not elucidate them, or correlate them with those in the outer cornea.

## Summary

A type of corneal dystrophy not previously described was found in both eyes of a 41-year-old man. A diffuse opacity in the anterior third of the stroma consisted of an accumulation of minute, slightly refringent dots. Partial penetrating keratoplasty performed on both eyes yielded specimens which, when examined histologically, showed (1) that the granules consisted of an amorphous material containing nucleic acid and hemosiderin, and (2) that Descemet's membrane was replaced by, or transformed into, a thick membrane composed of two distinct layers with different staining properties. The condition is regarded as a nonsystemic form of hemochromatosis which affects only the eye.

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# SPONTANEOUS CONGENITAL IRIS CYST

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This paper presents a case of spontaneous congenital iris cyst. In addition, the microscopic, ultramicroscopic, autoradiographic, and free amino acid findings of the cyst are also reported.

## CASE REPORT

This Negro boy was born to a 20-year-old woman, gravida 3, para 3, by forceps delivery on March 19, 1969. His birth weight was 3.17 kg and he had an Apgar rating of 10 at five minutes. On examination, the infant was adjudged to be normal and he was discharged at three days of age. He was readmitted eight weeks of age with a diagnosis of diarrhea and dehydration. At that time, the left eye, which had remained closed for the previous three weeks, revealed an abnormality. An examination revealed a normal right eye and a bilobated, slightly turbid, pigmented cystic structure which occupied about the lower half of the anterior chamber of the left eye. It touched the endothelium of the lower cornea and was present on the surface of the iris. Over a period of two weeks, the cyst appeared to fill 75% of the anterior chamber (Fig. 1). The horizontal corneal diameter in both eyes was 11 mm, while the intraocular pressure (Schiøtz) was two scale readings higher in the left eye than in the right. Under general anesthesia (halothane), a limbal-based conjunctival flap was laid inferior from four to six o'clock. A syringe with a 27-gauge needle was used to aspirate 100 ml of fluid from the cyst through a 4 mm incision of the limbus. Smooth, non-toothed forceps were used to bring the cyst out through the opening. The cyst appeared to be attached to the inferior mid-portion of the iris and a sector iridectomy was made inferiorly to remove the attachment of the cyst with the iris. The cyst was not attached to the pupillary margin and there was no lens defect. Following surgery, the inferior cornea of the left eye was hazy and by three months after surgery the inferior cornea was slightly cloudy, the intraocular pressure was 7/7 (7.5) mm Hg and a small semitransparent mass was noted at six o'clock with a contact lens. One year later this mass was not further enlarged.

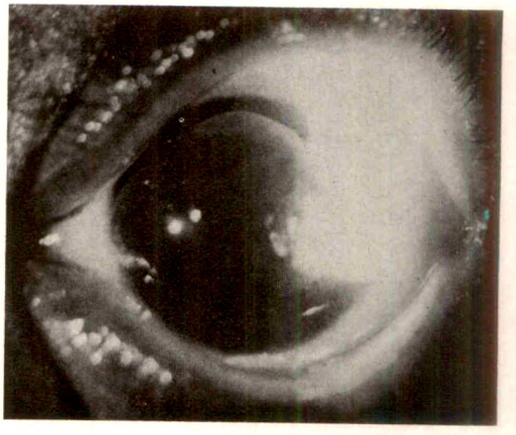


Fig. 1 (Roy and Hanna). Left eye, with bilobated, slightly turbid and pigmented cystic structure occupying lower 75% of anterior chamber. Light at superior temporal limbus is artifact.

## MATERIALS AND METHODS

On removal of the cyst, the tissue was immersed in a solution of tissue culture medium (TC-199) containing 1 μCi/ml of $^{3}$H-thymidine and 5μCI/ml of $^{3}$H-1-leucine both of sp. act 5 Ci/mmole.* After one hour's incubation at 37°C, the tissue was fixed for one day in freshly prepared 4% formaldehyde. The tissue was cut into six pieces and stained with osmium tetroxide and then embedded in epoxy (Araldite) plastic for microscopic, ultramicroscopic, and autoradiographic studies. The thick sections (0.1 to 4μ) were usually stained with toluidine blue, the thin sections (about 0.06 μ) were stained with uranyl acetate and lead citrate, and for autoradiography thick sections were coated with NTB2 Kodak liquid emulsion.[1] The cyst fluid sample was precipitated with 15% (w/v) aqueous sulfosalicylic acid, centrifuged and subjected

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* Nuclear-Chicago Corp., Des Plaines, Illinois.

Fig. 3 (Roy and Hanna). Normal iris tissue adjacent to iris cyst which contains pigmented epithelial cells on the posterior surface lower right corner (PE), smooth muscle cells in center (M), and pigmented stromal cells, upper left (toluidin blue, ×800).

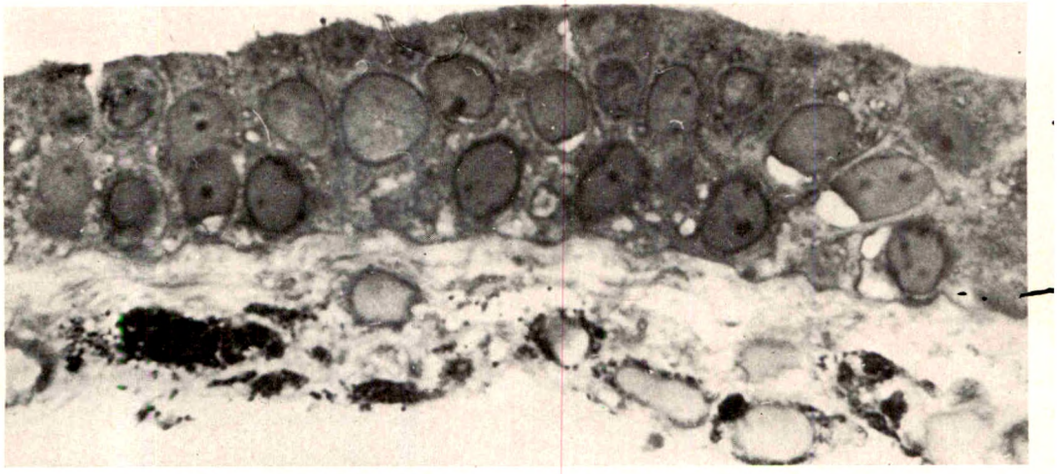


Fig. 2 (Roy and Hanna). Iris cyst wall with two to three layers of nonpigmented epithelial cells outermost with one or two layers of pigmented stromal cells (toluidine blue, ×900).

to ion exchange chromatography, using the Beckman Spinco Model 120C amino acid analyzer.[2]

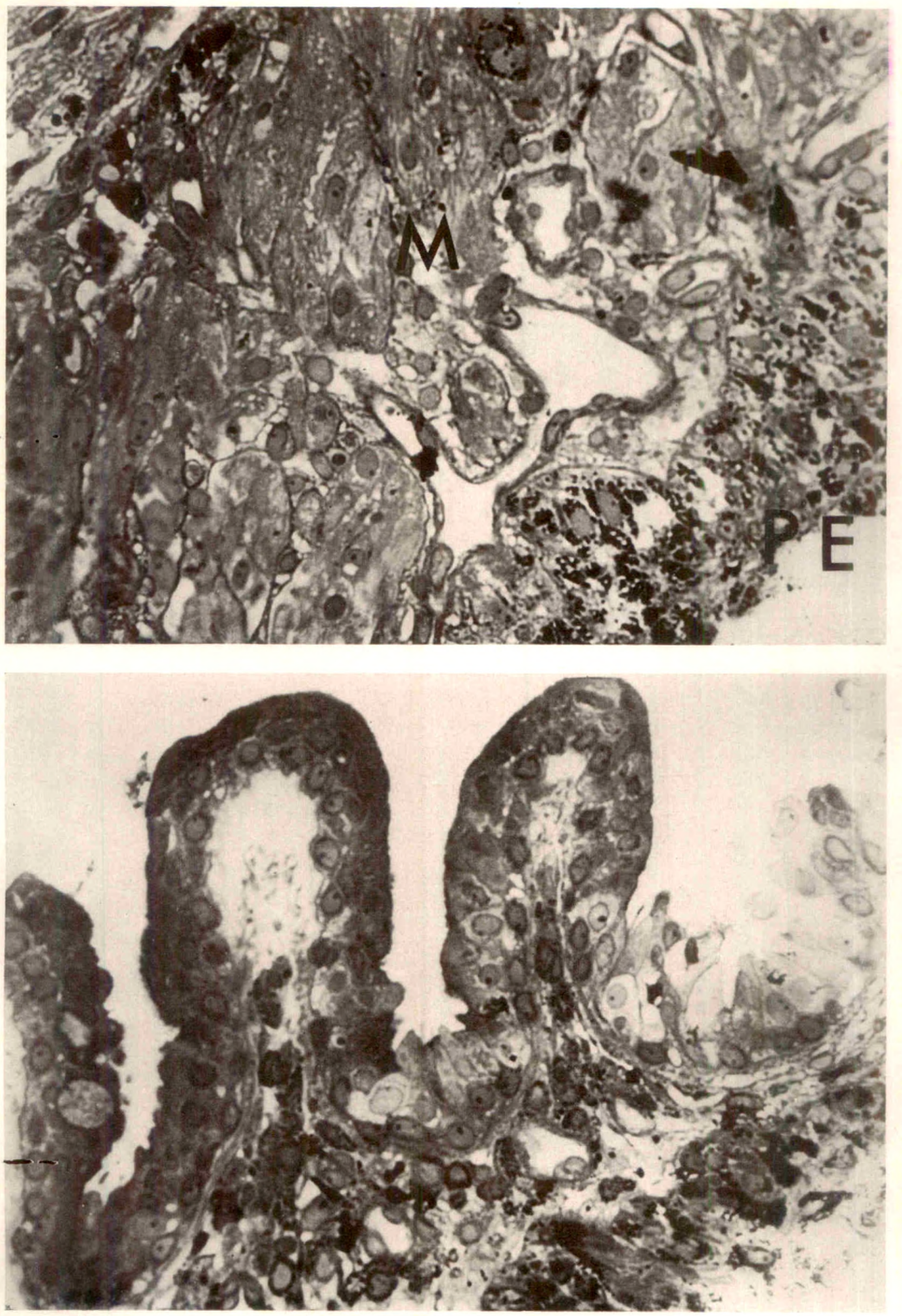
## Results

The cyst wall consisted of two or three layers of nonpigmented epithelial cells on the anterior side overlying one or two layers of pigmented cells (Fig. 2). The cyst was attached to the anterior surface of the iris below which were located normal appearing iris cells (Fig. 3). On the posterior side, remnants of the embryonic ciliary processes were found at the root of the iris (Fig. 4).

The epithelial cells covering the cyst took on many shapes. The innermost epithelial cells contained larger round nuclei and they closely resembled the basal epithelial cells of the cornea. No goblet or mucin cells were found.

The amino acid leucine is incorporated almost exclusively into newly synthesized protein. To estimate the relative rates of overall protein synthesis by various cell types, the cyst was incubated for a short period of time in leucine with a radioactive tracer ($^3$H-leucine). The autoradiograph was used to estimate the relative uptake of the radioactive

Fig. 4 (Roy and Hanna). Posterior surface of iris containing villi projecting into the posterior chamber These villi appear to be remnants of the embryonic ciliary process that may extend to the posterior surface of the iris. The surface of the villi are covered with nonpigmented epithelial cells. The outermost epithelial cells are covered by microvilli. Inside the villi are brightly red-staining collagen fibers (the red stain is so light that it appears in this photograph as white). Below the collagen layer are pigmented stromal cells. Further toward the pupil, the nonpigmented epithelial cells and villi disappear and become pigmented epithelial cells on the posterior side of the iris (basic fuchsin and methylene blue, ×800).


M
PE

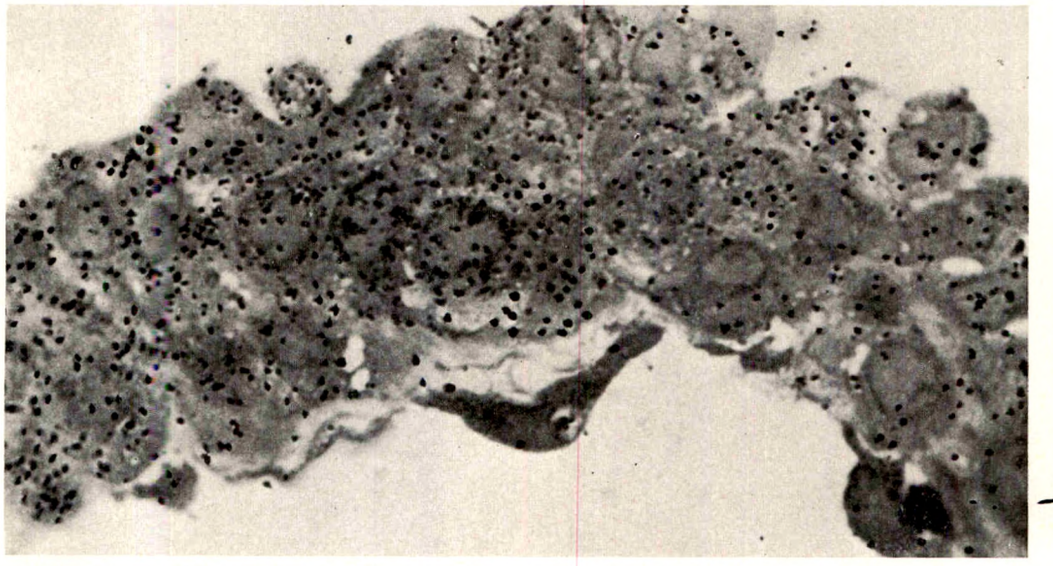


Fig. 5 (Roy and Hanna). The number of reduced silver grains (black dots) overlying the incorporating $^{3}$H-leucine into protein was higher for epithelial cells than for the pigmented stromal cells (inferior portion of photograph). In this autoradiographic photograph the focus is on the silver grains, and as a result the possibly confusing melanin granules are out of focus (autoradiogram stained with toluidine blue, ×900).

leucine taken up into protein. The cells of the cyst incorporated $^{3}$H-leucine into protein (Figs. 5 and 6). There was a relatively high grain count from the autoradiogram over the individual epithelial cells of the cyst that was similar to that of normal epithelial cells of the cornea.[3]

The free surface of the epithelial cells contained microvilli (Figs. 7-10). The cytoplasm of the epithelial cells contained various types of junctions, i.e., desmosomes, tight and gap junctions (Figs. 8-11), and intracellular filaments (Figs. 7-14). Similar junctions between stromal cells or epithelial and stromal cells were not noted (Figs. 11, 12, and 15) and the extracellular space between the epithelial and stromal cells contained banded filaments (Figs. 12-13).

The pigmented stromal cells of the cyst contained nuclei that were of varying shapes (Figs. 2, 12, and 15). These cells incorporated $^{3}$H-leucine into protein to give a low grain count in comparison with the epithelial cells of the cyst (Figs. 5, 6). These stromal cells incorporated $^{3}$H-leucine at a rate comparable to the stromal cells of the cornea.[3] The pigmented stromal cells were surrounded by collagen fibrils (Figs. 12, 13, and 15). These pigmented stromal cells did not have the characteristics of the pigment epithelial layer found on the posterior surface of the iris (Fig. 3). A piece of the iris that was tightly attached to the cyst was removed with the cyst. This iris tissue contained two layers of pigmented epithelial cells on the posterior surface, several layers of nonpigmented epithelial cells over the anterior surface and heavily pigmented and lightly pigmented (stromal) cells in the remainder of the tissue along with muscle cells (dilator iris) above the pigmented epithelium (Fig. 3).

Only a few mitotic figures were observed in the sections of the cyst. Only an occasional basal epithelial cell, and rarely a stromal cell, of the cyst incorporated $^{3}$H-thymidine into newly forming DNA. This indicates that a slow rate of cell division was taking place in the cells of the cyst compared to basal epithelial cells of the normal cornea that are undergoing a moderate rate of cell turnover.[3]

The piece of iris tissue adjacent to the cyst contained several layers of nonpigmented

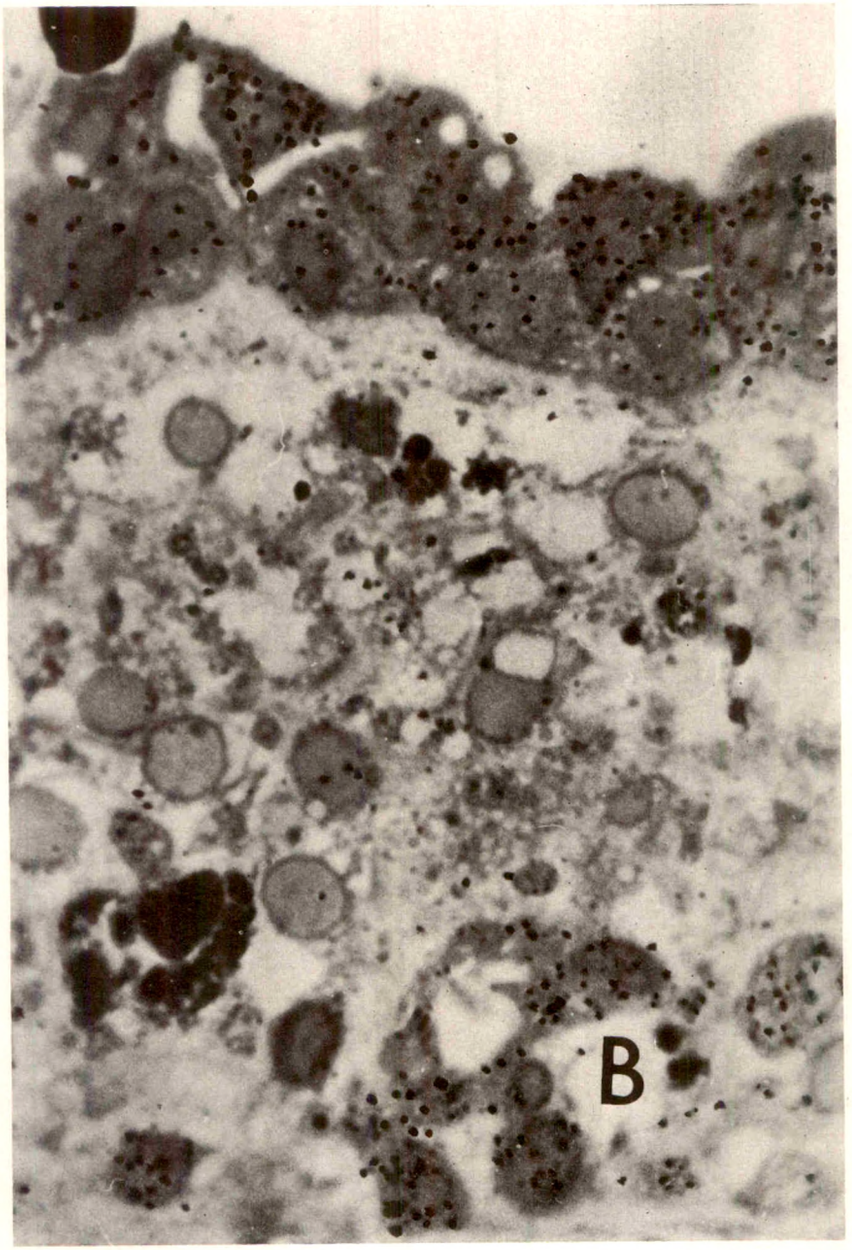



Fig. 6 (Roy and Hanna). The number of reduced silver grains over the endothelial cells surrounding a blood vessel (B) that had incorporated $^{3}$H-leucine into protein was similar to the number of reduced silver grains over the surface epithelium (top) overlying the iris (autoradiogram stained with toluidine blue, ×900).

epithelial cells on the anterior surface and two layers of heavily pigmented epithelial cells on the posterior surface. Between these layers were pigmented stromal cells. Heavily and lightly pigmented stromal cells were present beneath the epithelial layer (Fig. 15). These stromal cells were not generally in contact with adjacent cells. Collagen fibrils were found between the stromal cells and no cell junctions or tonofibrils were found.

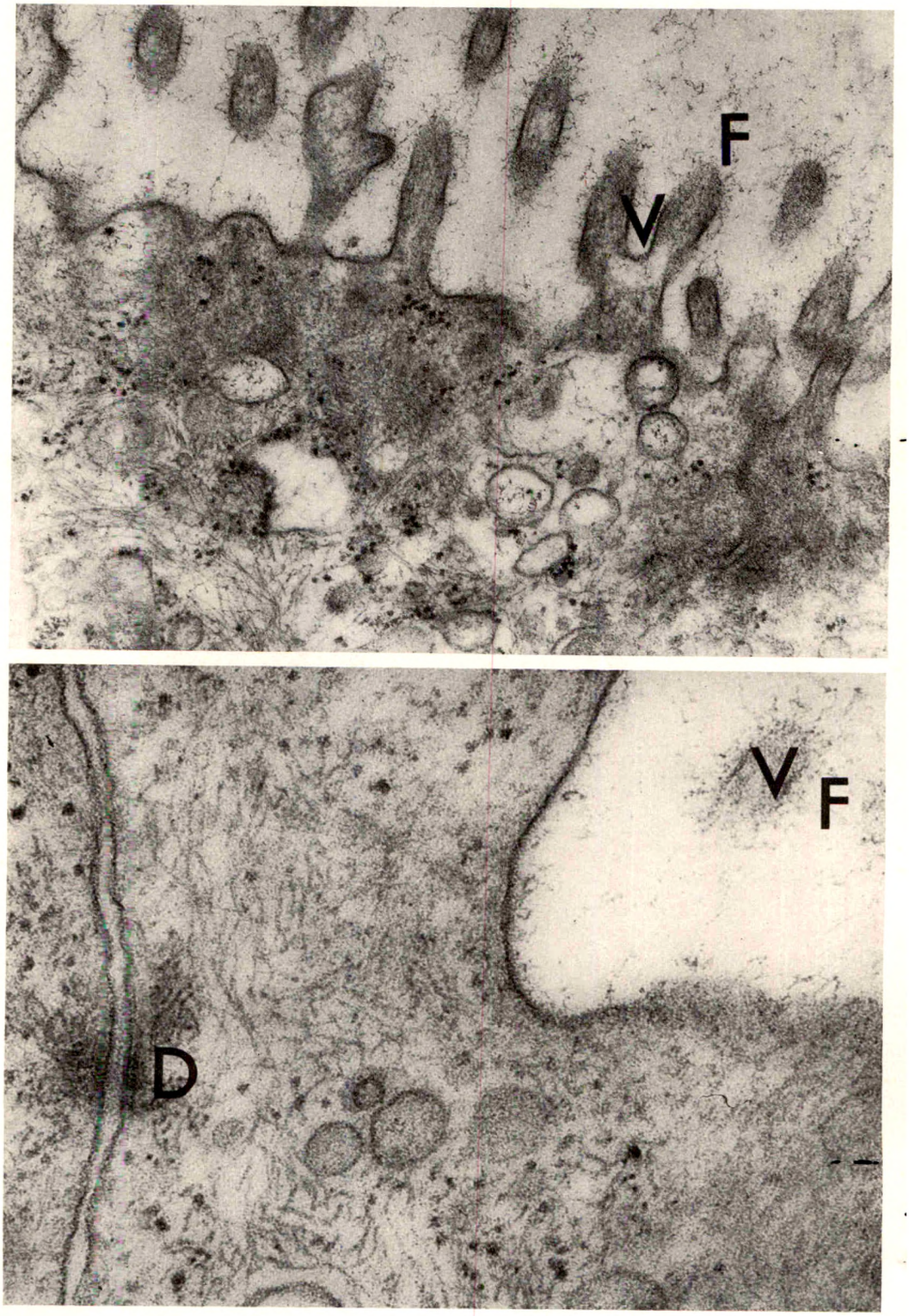

F
V
V
F
D

Fig. 7 (Roy and Hanna). The surface epithelial cells of the cyst contain striated or brush borders or microvilli (V). These microvilli are covered with plethora of delicate branching filaments (F) which forms an almost continuous coating. These filaments appear to be continuous with the unit membrane of the microvilli (×45,000).

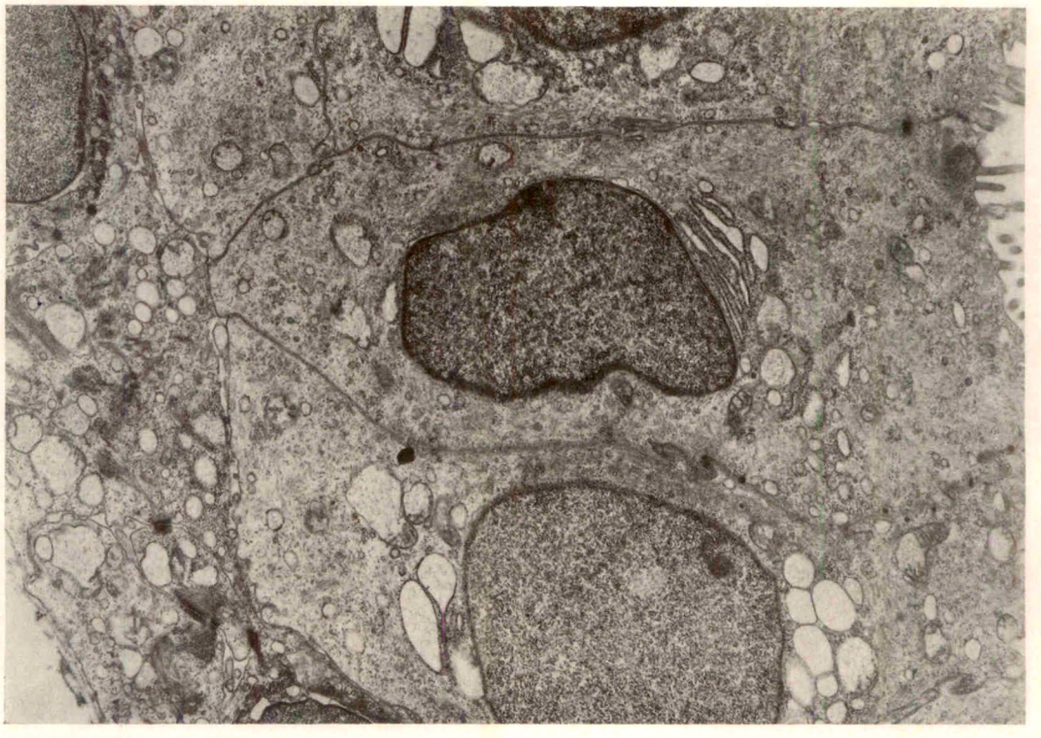


Fig. 9 (Roy and Hanna). Epithelila cells of cyst sectioned through area shown in Figure 2. Note the microvilli on the right side ×15,000).

The anterior chamber fluid contains a full spectrum of free amino acids similar to that found in the peripheral blood. The cyst itself, being an almost avascular sphere, may contain a fluid that has limited nutrients. The concentration of free amino acids in the cyst fluid was low.

Free amino acids are presented in Table 1. With the exception of histidine and cystine, the concentration of free amino acids in the aqueous humor of the adult human[2] was in all cases higher than that of the cyst.

## Comment

The origin of spontaneous iris cysts is still controversial.[4-7] Since both the cyst from the iris stroma and from the neural epithelium may occur in the stroma of the iris, Duke-

Fig. 8 (Roy and Hanna). Junction between two epithelial cells, left center, demonstrating desmosome (macula adherens) (D) surrounded by prominent tonofibrils. Part of a microvillus (V) with branching filaments (F) can be seen in upper right corner. Dark black spots throughout the cell are ribosomes (×100,000).




Fig. 10 (Roy and Hanna). Surface epithelium of the cyst contain unusually long microvilli and typical microvilli, cell junctions (tight junction, zonula occluden) (T), and many ribosomes (×45,000).

Elder[4] states that "differentiation between them on clinical grounds is impossible, and on histological grounds is difficult, the existence and separation of the two types rest more upon a theoretical than on an observational basis." Even with electron microscopic studies, we feel that one cannot positively determine how the nonpigmented epithelial cells arrived over the stromal cells of the cyst. The epithelial cells covering the cyst and part of the iris appear to be typical epithelial cells from the standpoint of ultrastructure with numerous polysomes, tonofibrils, desmosomes, and the high rate of incorporation of leucine into protein compared to adjacent stromal cells. The pigmented fibrocytes of the cyst contain intracellular collagen fibrils of various sizes. These cells could have a similar origin as did the stromal cells of the iris to which the cyst was at-

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Fig. 12 (Roy and Hanna). Lack of contact between pigment stromal cells on lower right and nonpigmented epithelial cells on upper left. The upper right shows collagen (C) fibrils (×15,000).

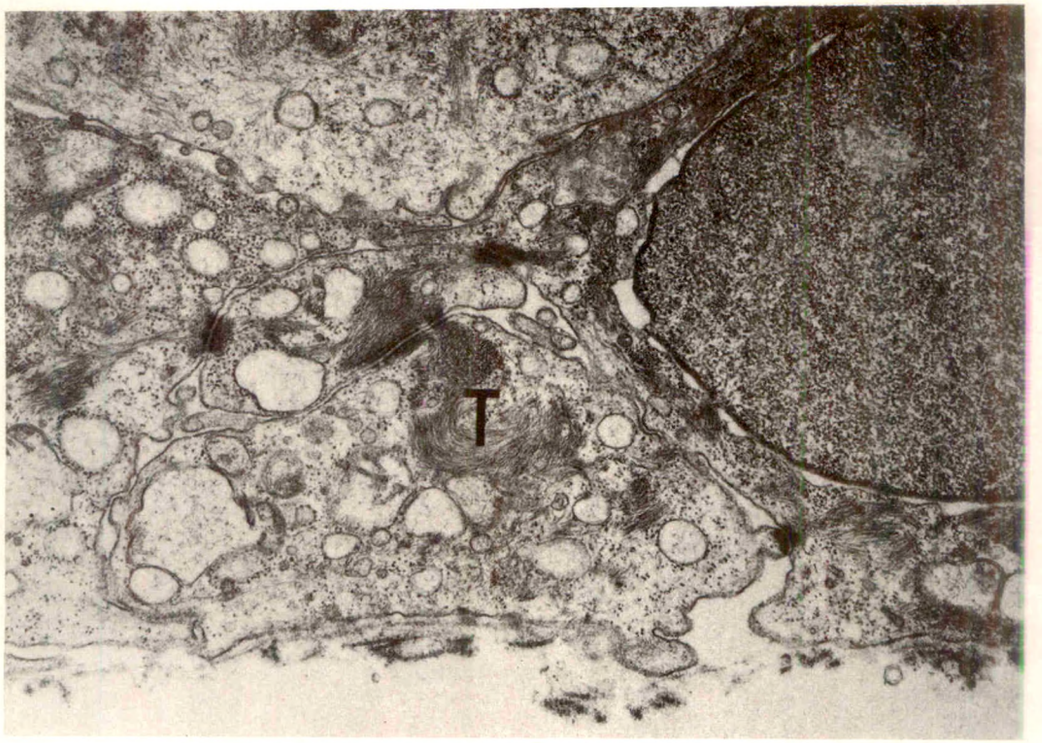
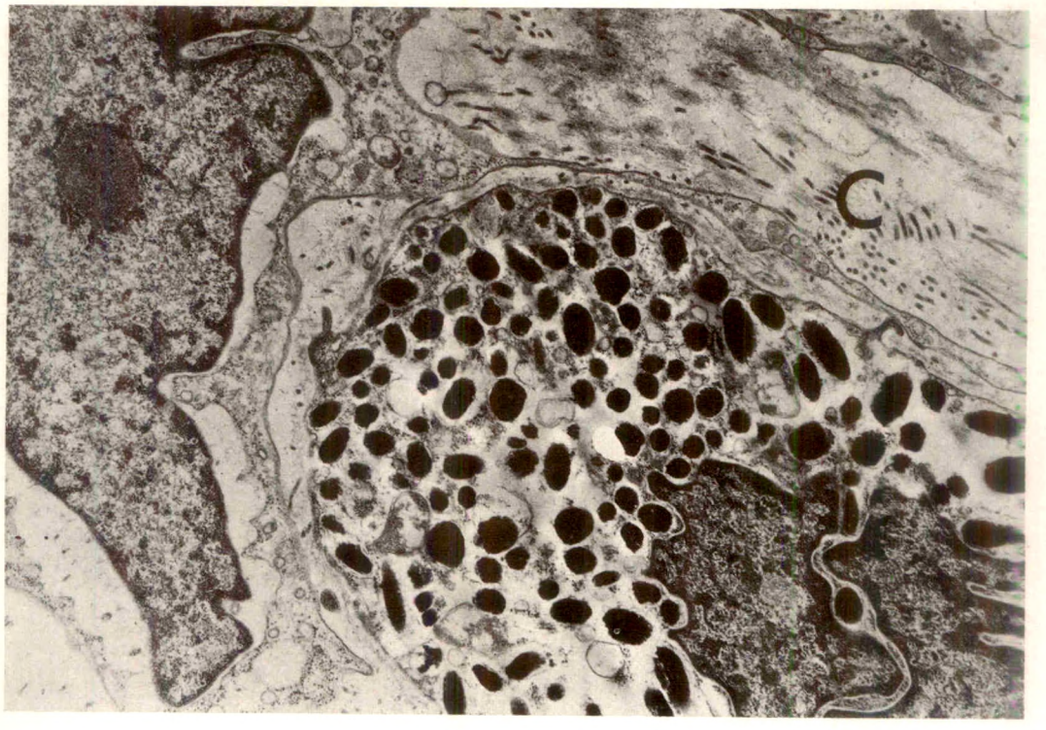



Fig. 11 (Roy and Hanna). Epithelial cells adjacent to pigmented cells or iris cyst from Figure 9, illustrating desmosomes with apparently innerconnecting tonofibrils (T) (×15,000).



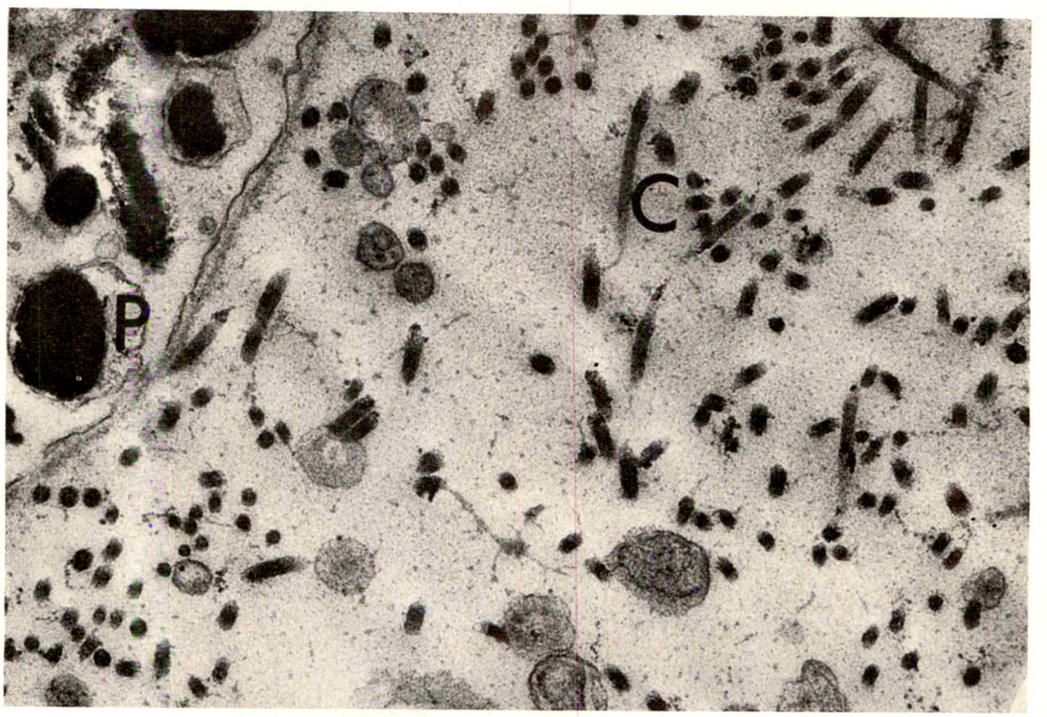
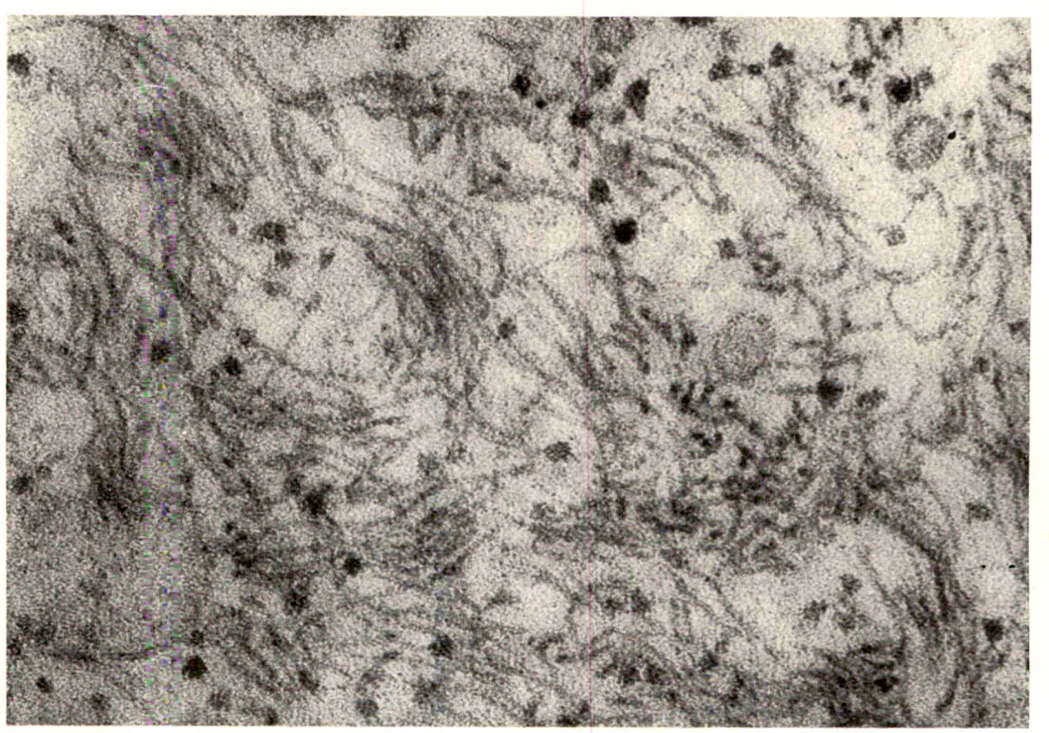



Fig. 13 (Roy and Hanna). Extracellular space surrounding a pigment stromal cell of Figure 12 at upper left, illustrating pigmented vesicles (P) and collagen fibrils (C) (×30,000).



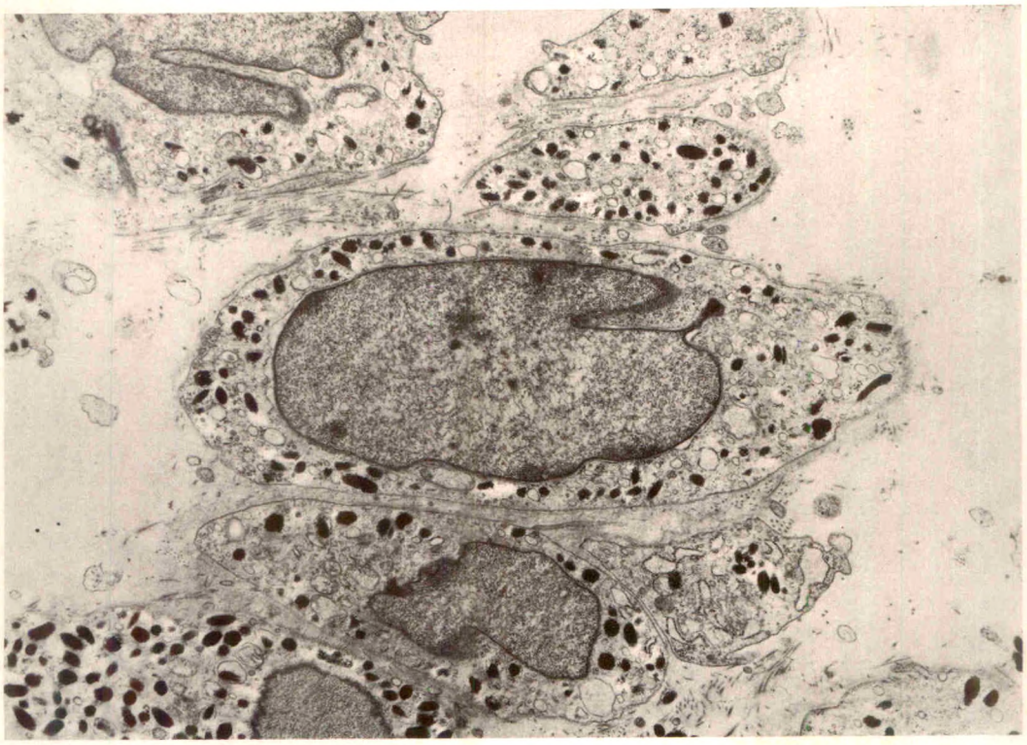


Fig. 15 (Roy and Hanna). Pigmented stromal cells near junction of iris and cyst near the pupil showing lack of cell junctions. Instead these cells are surrounded by extracellular collagen fibrils (×5,000).

tached. The resultant of the uptake and incorporation of $^{3}$H-leucine into protein by pigmented cells of the cyst and stromal cells of the noncystic part of the iris were also similar.

Several possibilities should be considered in the histogenesis of the cyst: It may derive from (1) pigment epithelium, (2) conjunctival epithelium, (3) ectopic lacrimal gland ductal epithelium, (4) from nonpigmented neuroepithelium, or (5) from iris stroma. Since the epithelial layer of this cyst lacks pigment granules, mucous glands (goblet cells),[6] and glandular tissue, the first three possibilities are unlikely. The most likely histogenesis of this spontaneous congenital cyst is nonpigmented neuroepithelium covering stromal cells derived from the iris.

Fine[7] reported a free-floating pigmented cyst in the anterior chamber of a 22-year-old man. In his patient, the cyst was composed of pigmented epithelial cells that were delineated on one side by a basement membrane and contained diastase sensitive granules (glycogen deposits). In the study reported here, neither pigmented epithelial cells, a basement membrane, nor glycogen deposits were detected in the cells of the cyst.

The extent and length of the microvilli covering the epithelial cells to the cyst were extraordinary. These microvilli were visible

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Fig. 14 (Roy and Hanna). Enlarged view of filaments and the rounded ribosomes from an epithelial cell (×100,000).

TABLE 1

COMPARISON OF AMINO ACID CONCENTRATIONS (MG/LITER) IN AQUEOUS FLUID OF 19 ADULTS JUST PRIOR TO CATARACT EXTRACTION AND IN THE FLUID OF THE CYST

| Amino Acid | X. Aqueous | ±S.D. Aqueous | Cyst Fluid |
|---|---|---|---|
| 1. Asparagine and glutamine | 0.708 | 0.059 | 0.0001 |
| 2. Alanine | 0.330 | 0.032 | 0.0001 |
| 3. Valine | 0.250 | 0.017 | 0.0043 |
| 4. Serine | 0.180 | 0.040 | — |
| 5. Threonine | 0.129 | 0.063 | — |
| 6. Leucine | 0.127 | 0.025 | 0.0004 |
| 7. Lysine | 0.123 | 0.031 | — |
| 8. Arginine | 0.110 | 0.025 | — |
| 9. Phenylalanine | 0.101 | 0.017 | — |
| 10. Isoleucine | 0.098 | 0.050 | 0.0003 |
| 11. Tyrosine | 0.093 | 0.021 | 0.0001 |
| 12. Taurine | 0.061 | 0.019 | 0.0007 |
| 13. Histidine | 0.056 | 0.021 | 0.0660 |
| 14. Glycine | 0.048 | 0.033 | 0.0004 |
| 15. Ornithine | 0.040 | 0.015 | — |
| 16. Glutamic acid | 0.021 | 0.014 | — |
| 17. Aspartic acid | 0.012 | — | 0.0001 |
| 18. 2-amino-iso-butyric acid | 0.011 | — | — |
| 19. Methionine | 0.027 | 0.009 | 0.0001 |
| 20. Tryptophane | 0.002 | — | — |
| 21. Proline | 0.002 | — | — |
| 22. Citrolline | 0.002 | — | — |
| 23. ½ Cystine | 0.001 | — | 0.0043 |
| ½ Cystine and urea | 2.714 | 0.785 | 0.0080 |

under microscopic observation. Such villi have not previously been reported for iris cysts. The presence of very low free amino acids in the fluid of the cyst, compared to the normal anterior chamber fluid, suggests that the cyst contained no opening to the anterior chamber, or at the most, only a small opening. The microvilli are similar in structure to the absorptive cells of the small intestine[8] and the concentration of nutrients inside the cyst might be expected to be low. It is of interest that in the presence of a very low free amino acid concentration, the cells lining the inside of the cyst were viable. Possibly this is due to the fact that the pigmented cells lining the cyst are undergoing a low rate of protein synthesis as indicated by the relatively small uptake and incorporation of $^{3}$H-leucine into the protein of these cells.


## SUMMARY

A spontaneous cyst in the anterior chamber and attached to the iris was found in an eight-week-old infant. Microscopic, ultramicroscopic, and autoradiographic features of the cyst are presented. The cyst wall is composed of several layers of pigmented stromal cells covered by multiple layers of nonpigmented epithelial cells. The surface epithelial cells were covered with unusually long microvilli and there was no evidence of goblet cells. An occasional epithelial cell was observed to be undergoing DNA synthesis and a few mitotic figures were found; however, these cells readily incorporated radioactive leucine into protein. The free amino acid content of the cyst fluid was low compared to the free amino acids in the aqueous fluid. We concluded that the cyst developed from the anterior surface of the iris and the cells covering it are derived from the nonpigmented neuroepithelium.



## ACKNOWLEDGMENTS

Jerome Sherman and Catherine Dodd, Department of Anatomy, aided in the electron microscopic observation, and Juan Sanchez, Department of Ophthalmology, determined the free amino acid composition of the cyst. We wish to acknowledge their contributions to this study.


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# LATE RESULTS OF KERATOPLASTY FOR FUCHS' DYSTROPHY

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The success of penetrating keratoplasty in Fuchs' dystrophy is well documented. Clear grafts have been reported in from 70[1] to 85%[2] of cases, with a considerable difference between those with early disease as compared to those with advanced disease (good results expected in 85% of early cases but only 50% of advanced cases).

Most of the patients, however, have been followed for a relatively short period of time. Stocker and Irish,[3] in a recent report, suggest that the long-term fate of these grafts is quite poor. All of the 12 cases they reported became cloudy in one to eight years.

The purpose of this study is to report the long-term follow-up of penetrating keratoplasties for Fuchs' dystrophy and to examine the causes of failure in those grafts which became cloudy.

## MATERIAL

This report reviews a total of 193 penetrating grafts done on 150 patients with Fuchs' dystrophy. All operations were performed by one surgeon (M.F.). Follow-up ranged from six months to 15 years. This study reports all patients in which the diagnosis of Fuchs' dystrophy was made, including cases with preoperative complications, aphakia, regrafts, combined graft-cataract procedures, and all postoperative complications. In cases in which the patient was not available for follow-up observation, information was obtained from the referring ophthalmologist by letter.

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The indication for keratoplasty was the existence of corneal edema in a degree which reduced the visual acuity in the better eye to 20/50 or less. The great majority of cases had a corrected acuity of 20/200 or less. No cases were accepted for keratoplasty with simple endothelial dystrophy without stromal edema.

Preoperatively the patient was placed into one of three prognostic categories: I. mild (area of edema less than 6 mm), II. moderate (area of edema 7-8 mm), and III. severe (cornea completely edematous or in need of reoperation, anterior synechiae, glaucoma, aphakia with complicating factors).

## DONOR MATERIAL

Since specific information on donors has been recorded only for the past four years, this information is not available on all patients. The practice has always been, however, to use cadaver eyes removed up to 10 hours after death and refrigerated at 2-4° C in a moist chamber. Selection has been random for all penetrating keratoplasties, without regard to age of donor. The mean age of donor material used for all types of grafts has been 61 years.[4] Ninety-nine percent of donor corneas were transplanted within 48 hours of death; 51% were transplanted within 24 hours, and 39% between 25 and 36 hours post mortem.

## SURGICAL TECHNIQUE

The technique used is essentially as previously described for phakic[2] and for aphakic patients.[5] Most grafts were 7 or 7.5 mm in diameter, except for a few 8 mm in size.

## RESULTS

The overall incidence of clear grafts in Fuchs' dystrophy is 85% and the incidence of clear grafts eight years or longer after keratoplasty is the same (85%). A clear

TABLE 1

RESULTS OF GRAFTS IN FUCHS' DYSTROPHY (193 CASES)

| Follow-up in Years | I* | | II* | | III* | | Totals |
|---|---|---|---|---|---|---|---|
| | Clear | Cloudy | Clear | Cloudy | Clear | Cloudy | Clear/Cloudy |
| One-half | 7 | 1 | 5 | | 9 | 4 | 21/5 |
| One | 12 | | 12 | 2 | 4 | 1 | 28/3 |
| Two | 15 | | 7 | 3 | 6 | 1 | 28/4 |
| Three | 9 | 1 | 3 | 3 | 6 | 1 | 18/5 |
| Four | 4 | | 5 | | 1 | 5 | 10/5 |
| Five | 1 | | 10 | | 8 | 4 | 19/4 |
| Six | 2 | | 9 | | 2 | | 13/0 |
| Seven | 4 | | 4 | | 2 | | 10/0 |
| Eight | 4 | | 4 | 1 | 2 | | 10/1 |
| Nine | | | 2 | | 1 | 2 | 3/2 |
| Ten | | | 1 | | 1 | | 2/0 |
| Over ten | | | | | 2 | | 2/0 |
| Totals and % | 58 (96.7%) | 2 | 62 (87.6%) | 9 | 44 (71%) | 18 | 164/29 (85%/15%) |

* Prognostic classification.

graft was considered to be one in which there was no biomicroscopic evidence of central or peripheral edema and in which the transparency permitted vision of 20/40 or better. A subephithelial haze of varying severity is present in many homografts performed for all types of corneal disease and usually does not reduce the visual acuity appreciably. Such grafts were classified as clear if the visual acuity with correction was 20/40 or better. Corneas associated with cataract, or with ocular abnormalities, were classified as clear if their transparency was compatible with 20/40 vision. Opacities surrounding the suture sites were not considered in the classification. Table 1 details the results by year and according to preoperative prognostic classification. When studied according to prognostic classification, even the least favorable cases have an overall result of 71% clear grafts, with the eight patients followed more than eight years having 75% (six out of eight) clear grafts. The most favorable category, Group I, has 96.7% overall incidence of clear grafts (Table 2).

*Analysis of failed grafts*—There were 29 grafts of the 193 which became cloudy and these are analyzed as to the cause of failure (Table 3). These 29 grafts were performed in 24 eyes of 22 patients. Ten patients had two keratoplasties in one eye, five of which became cloudy and five of which remained clear for a follow-up ranging from six months to eight years. Two of the five in which the second graft failed had a third graft done, and these two have remained clear for one and two years, respectively.

When studied according to prognostic groups, two failures were in Group I (3.3%), nine failures were in Group II (12.5%), and 17 failures were in Group III (27.9%).

*Group I (mild)*—Of the two cloudy grafts in Group I, one had a graft reaction at one month but was regrafted, with the second graft remaining clear for eight years thus far. The other in Group I had a combined graft-lens extraction which was complicated postoperatively by pupillary block and subsequent glaucoma. This graft became cloudy after two years.

TABLE 2

GRAFTS FOLLOWED EIGHT TO 15 YEARS
(20 Cases)

| Outcome | I* | II* | III* | Total |
|---|---|---|---|---|
| Clear | 4 | 7 | 6 | 17 (85%) |
| Cloudy | 0 | 1 | 2 | 3 (15%) |

* Prognostic group

*Group II (moderate)*—Of the cloudy grafts in Group II, two were cloudy from the first postoperative day, which is attributed either to poor donor tissue or technical problems at the time of surgery. One of these two, however, had a combined graft-lens extraction with hemorrhage on the posterior surface of the graft. Two of the nine were clear until they had lens extractions one year and two years, respectively, after the keratoplasty. Both of these cataract extractions were complicated. Three were cloudy after graft reactions, occurring at one month, one year, and six months post-grafting.*

The remaining two patients had a chronic iridocyclitis following surgery with clouding of the graft at six months and three years.

*Group III (severe)*—There were 17 opaque grafts of the total of 61 grafts in Group III (27.9%). Two of this group were clear for two and five years postoperatively at which time they had a lens extraction with clouding of the graft following this procedure. One of these had a second graft which has remained clear one year. Graft reactions leading to clouding of the graft occurred in five patients. One of this group was a re-operation for a previous graft reaction in that eye (one month). The two graft reactions which occurred at nine months were both in the same patient, one in the right eye and one in the left eye. The one occurring at two years was a regraft after a failure due to iritis with anterior synechias. Of the four grafts which were cloudy from the first post-operative day, one was a combined graft-lens extraction in a patient with glaucoma who had had prior glaucoma surgery, one was a regraft of a previous graft reaction, one was a regraft following failure due to trauma of lens extraction, and the fourth was in an aphakic patient. The postoperative course in two patients was complicated by uncontrolled glaucoma; one of these patients was aphakic with preoperative glaucoma and vitreous adhesion. The other was also aphakic with iris adhesions and a dense pupillary membrane. For the remaining five patients, there was insufficient information from the referring physician to explain the failure. It was felt, however, that they should be included in this study.

* The criterion for the diagnosis of an immune homograft recation was the sudden onset of edema in an uncomplicated graft which had been perfectly clear for at least two weeks from the time of operation, accompanied by a mild to moderate iridocyclitis. The diagnosis was not made when the edema was preceded by a severe uveitis, uncontrolled glaucoma or evidence of technical complications.

TABLE 3

CAUSES OF GRAFT FAILURE

| Cause | No. Patients |
|---|---|
| Homograft reaction | 9 |
| Operative failure* | 6 |
| Subsequent lens extraction | 4 |
| Postoperative glaucoma | 3 |
| Postoperative iridocyclitis | 2 |
| No explanation available | 5 |
| Total | 29 |

* Cloudy first postoperative day.

### CAUSES OF FAILURE

The causes for failure in all groups are summarized in Table 3.

Immune homograft reactions resulting in permanently opaque grafts occurred in nine patients, a 4.6% incidence, as compared to the usually accepted incidence of 8 to 10%. The actual incidence of graft reactions was 12%, but about half of these responded to corticosteroid treatment and remained clear. Routine corticosteroid treatment to prevent immune reactions consisted of the daily instillation of a corticosteroid-antibiotic ointment at the time of surgery and with the daily dressing. If manipulation of the iris was required during the keratoplasty (iridectomy, freeing of adhesions, etc.), a subconjunctival injection of 20 mg of repository methyl-prednisilone was made at the close of the operation. When the eye showed more

than the average postoperative reaction corticosteroid drops were instilled three to six times daily in addition to the ointment. This medication was reduced to a maintenance dose as soon as a response was obtained. Topical corticosteroid drops were continued one to three times daily for three to four months following operation, depending on the degree of irritation.

In a suspected or actual immune reaction, topical corticosteroid drops (1% prednisilone or equivalent) were given every one or two hours and a subconjunctival injection of 20 mg of repository methyl-prednisilone every 10 to 14 days to a maximum of three injections, depending on response.

Systemic corticosteroids were not used since we have not observed any advantage from systemic medication over intensive local medication in controlling the homograft reaction.

Of the four grafts lost following subsequent lens extractions, one cannot guess how long they would have remained clear. This must still be regarded as an exogenous factor in graft survival. Grafts which are opaque from the first postoperative day, as mentioned previously, are felt to be due either to poor donor material or unsuspected surgical trauma to the endothelium. Gross technical problems should be obvious to the surgeon at the time of surgery.

The emphasis again is made that the majority of failures was in patients in the poorest prognostic category, and here there was still an incidence of 71% clear grafts. For those grafts followed eight years or longer there is an overall prognosis of 85% success with a low of 75% success in those of the poorest prognostic classification.

Regrafts in cases of Fuchs' dystrophy appear to have about the same prognosis as regrafts in other categories of corneal opacities of similar severity. The important factors determining the result of the second graft are the presence or absence of complications such as adherent iris, glaucoma, and severe edema with vascularization. Table 4 summarizes the information on the 29 cloudy grafts in which 14 regrafts were performed. Nine of the regrafts were clear during the period of follow-up of one to eight years. It is of interest that of the 14 regrafts, 10 were performed within one year of the previously failed keratoplasty. This suggests that time alone is not a principal cause of graft failure in Fuchs' dystrophy.

## Discussion

No conclusive evidence has been presented to demonstrate whether corneal grafts for Fuchs' dystrophy remain clear because of persistence of the donor epithelium or because of repopulation of the graft with endothelium from the recipient. Polack's[6] studies showing persistence of isotopically labeled endothelial cells in rabbit corneal grafts for four years probably indicated that a combination of the two mechanisms is in operation. Our experience with keratoconus patients is similar to that of others, namely, that these grafts seem to have an unlimited lifetime. If one assumes persistence of donor epithelium to be the main factor, one could conclude that grafts in keratoconus should have the same prognosis as in Fuchs' dystrophy (or any other condition) when similar material is selected. In fact, one would be more careful in selecting young, healthy donors for keratoconus than for Fuchs' dystrophy, since the former group of patients has a much longer life expectancy.

To date there has been no direct evidence that donor endothelial cells in human homotransplantation survive in toto and indefinitely. Such evidence in the form of clear grafts from the opposite sex coming to histologic examination or karyographic study is very difficult to obtain but will ultimately be available. Indirect evidence such as the occasional occurrence of very late immune reactions is open to much criticism.

If the primary factor in graft survival were replacement by endothelium from the

TABLE 4

OPAQUE GRAFTS IN FUCHS' DYSTROPHY

| Case No. | Preoperative Prognostic Classification | Onset of Edema | Size of Graft (in mm) | Cause of Failure | Subsequent Procedures | Outcome | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | I | 1 month | 7 | IR* | Regraft | Clear | 8 years |
| 2 | I | 2 years | 7 | Glaucoma | | | |
| 3 | II | 3 years | 7 | Iridocyclitis | | | |
| 4 (and 14) | II | Postoperation | 7 | Operative failure† | Regraft | Cloudy | 2 years |
| 5 | II | 1 year | 7.5 | Subsequent lens extraction | Regraft | Clear | 1 year |
| 6 | II | 6 years | 7 | IR | | | |
| 7 (and 19) | II | 1 month | 7 | IR | Regraft | Cloudy | 1 month |
| 8 (and 24) | II | 6 months | 7.5 | Iritis with anterior synechias | Regraft | Cloudy | 2 years |
| 9 | II | 1 year | 7.5 | IR | | | |
| 10 (and 26) | II | 2 years | 7 | Subsequent lens extraction | Regraft | Cloudy | Postoperation |
| 11 | II | Postoperation | 7 | Combined graft-cataract operation with hemorrhage post-surface of graft | | | |
| 12 | III | ? | 7.5 | Unexplained | | | |
| 13 | III | Postoperation | 7.5 | Combined graft-cataract operation; previous glaucoma surgery | Regraft | Clear | 1 year |
| 14 | III | 2 years | 8 | Subsequent lens extraction, vitreous touch | | | |
| 15 | III | 5 years | 8 | Subsequent lens extraction with endophthalmitis | Regraft | Clear | 3 years |
| 16 | III | 1 year | 7 | Unexplained | | | |
| 17 | III | 3 years | 7 | Aphakia, adherent iris, pupil membrane, postoperative glaucoma | | | |
| 18 | III | 4 months | 7 | Operative failure | | | |
| 19 | III | 1 month | 7.5 | IR | | | |
| 20 | III | 3 months | 7.5 | Unexplained | Regraft | Clear | 2 years |
| 21 | III | 9 months | 7 | IR | Regraft | Clear | 3 years |
| 22 | III | 9 months | 7 | IR | | | |
| 23 | III | 1 year | 8 | Unexplained | | | |
| 24 | III | 2 years | 7 | IR | Regraft | Clear | 2 years |
| 25 | III | Postoperation | 7.5 | Operative failure | Regraft | Clear | 3 years |
| 26 | III | Postoperation | 7.5 | Operative failure | | | |
| 27 | III | 1 month | 7.5 | Aphakia, glaucoma, vitreous adhesion, postoperative glaucoma | | | |
| 28 (also 29) | III | 3 months | 7.5 | IR | Regraft | Cloudy | Postoperation |
| 29 | III | Postoperation | 8 | Operative failure | Regraft | Clear | 1 year |

* IR = immune graft reaction

† Operative failure = severe edema of graft on first postoperative day.

host, then one might expect a very restricted lifetime of grafts for Fuchs' dystrophy, since the endothelium is usually severely affected by the time a graft is performed. Our data do not seem to support this, since most graft failures were associated with other definite and recognizable causes. If there is a restricted lifetime of these grafts, the follow-up still has not been long enough to detect it.

The idea that there is no possibility of regeneration of endothelial cells from the recipient with Fuchs' dystrophy is open to question. In early cases, some competent cells are still present from which regeneration might conceivably occur, although ultimately these two might become dystrophic. The clinical observation that the results of penetrating keratoplasty in early cases with only central edema are much better than those in which the entire cornea is edematous tends to support this possibility.

On the basis of this material it is concluded that the prognosis of penetrating keratoplasty in Fuchs' dystrophy should be considered good.


## Summary

In 193 penetrating keratoplasties for Fuchs' dystrophy followed six months to 15 years, the incidence of clear grafts was 85%. In 20 grafts observed from eight to 15 years, the incidence of clear grafts was also 85%. A progressive failure rate with time was not present. Various postoperative complications (immune reactions, iridocyclitis, glaucoma, complicated lens extraction, etc.) were associated with the failure of 25 of the 29 cloudy grafts.


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# VALIDITY OF MacKAY-MARG APPLANATION TONOMETRY FOLLOWING PENETRATING KERATOPLASTY IN MAN

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Using the Goldmann tonometer, scarred, edematous and irregular corneas produce irregular circles making measurement of intraocular pressure impossible. Similarly, the Schiøtz tonometer was designed for use on corneas of a standard curvature and when used on diseased corneas produces misleading readings.[1] Recent studies[2,3] have indicated that MacKay-Marg electronic applanation tonometer readings of diseased and post surgery corneas are accurate. However, the alarmingly high pressures found in a large proportion of aphakic penetrating keratoplasty patients[3] has caused several experienced clinicians to question the validity of MacKay-Marg readings.

This study assesses the accuracy of the MacKay-Marg electronic applanation tonometer in penetrating keratoplasty patients by comparing its readings with simultaneous measurements made by cannulation of the anterior chamber.

## MATERIALS AND METHODS

Two patients scheduled for penetrating keratoplasty were chosen for this study.

The first, a 67-year-old white man with Fuch's dystrophy, underwent an intracapsular cryosurgical cataract extraction (without chymotrypsin) and an 8 mm penetrating keratoplasty. The corneal graft was sutured with 10-0 nylon running suture. Immediately after securing the transplant to the host (patient was still draped and the operating microscope in place), a 23-gauge needle connected by sterile vinyl tubing to a Sanborn transducer, was inserted into the anterior chamber. The intraocular pressure was varied by injecting a balanced salt solution through the graft wound. Continuous readings were recorded with the Sanborn transducer, and while the cannula remained in the anterior chamber, simultaneous measurement were taken with the MacKay-Marg tonometer. Tonometer readings were interpreted before the manometer readings were known, and then compared with the continuous pressure tracing.

The second patient, a 65-year-old white woman with aphakic bullous keratopathy, underwent an 8 mm penetrating keratoplasty. Using the same method as in the first patient, the intraocular pressure was measured immediately after securing the corneal graft to the host.

These patients had no complications from this procedure and their keratoplasties remained thin and clear.

## RESULTS

Since the keratoplasty wounds were tight and there was no leakage around the cannula, the manometer pressures tended to remain stable at each level between MacKay-Marg measurements.

There was an excellent correlation between the direct intraocular pressure measurements (manometer) and those taken by the MacKay-Marg applanation tonometer (Fig. 1). The 15 measurements covered a pressure range from 5 to 82 mm Hg and gave a slope of 0.956.

## DISCUSSION

Previous clinical studies have shown that while MacKay-Marg readings are accurate in diseased or scarred human corneas and in distorted animal corneas, both Schiøtz and Goldmann readings are inaccurate and mis-

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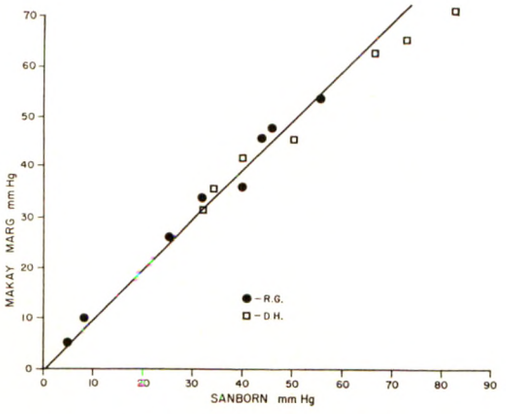



Fig. 1 (Wind and Kaufman). Comparison of intraocular pressure measurements obtained by direct cannulation of the anterior chamber to simultaneous measurements obtained with the MacKay-Marg tonometer.

leading.[1-3] The MacKay-Marg has proven accurate in measuring intraocular pressure in animals following penetrating keratoplasty,[2] and this study verifies that MacKay-Marg tonometry is accurate in patients following penetrating keratoplasty.

Although only two patients were studied, the number of measurements is significant and covers the range encountered clinically. In pressures elevated over 70 mm Hg, a greater discrepancy was noted than at lower pressures. However, even in those high ranges, the pressures correlated well. This study has verified that intraocular pressure measurements in human eyes after keratoplasty are possible, and can be accurate and reproducible. Theoretically, the electronic applanation tonometer readings are not affected by changes in corneal elasticity, since at the point of tracings (where the reading is taken) the corneal bending force is displaced from the plunger onto the probe shoulder.[4]

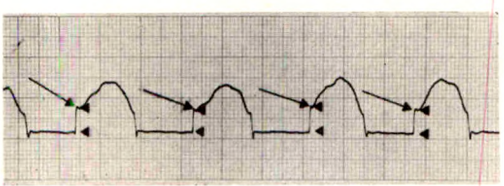


Fig. 2 (Wind and Kaufman). An appropriate reading curve exhibits an initial crest, a central maximum, and a final crest. The small arrows indicate pressure measure points. Note that good readings are serially repetitious and identical in pattern and size.

MacKay-Marg readings are reliable only for good tracings and are interpretable only if repeatable tracings with the proper configuration are obtained (Fig. 2). For example, to obtain accurate readings in eyes with a relatively flat cornea after surgery, great care must be taken to have the probe exactly perpendicular to the globe. If good reproducible readings cannot be obtained, the results cannot be interpreted. Occasionally, especially in early postoperative patients, (usually the first day after surgery), adequate readings cannot be obtained. In general, on diseased and recent postoperative eyes, a certain facility with the MacKay-Marg applanation tonometer is required to obtain interpretable pressure readings.

## Summary

Following penetrating keratoplasty in two patients, intraocular pressure readings with the MacKay-Marg applanation tonometer were compared with simultaneous readings taken by direct cannulation of the anterior chamber (Sanborn transducer manometer).

The readings correlated extremely well and verified the validity and importance of MacKay-Marg measurements in these and other cases where accurate Schiøtz or Goldmann readings are impossible.

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# ULTRAMICROSCOPIC ALTERATIONS IN CORNEAL EPITHELIUM IN CORNEAL GRAFTS

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Previous studies[1-3] have described the histologic alterations of the experimental corneal graft reaction as seen with the light microscope. It has been established that rejection of donor tissue starts after a sensitization period of about two weeks.[2] Also, the cellular elements participating in the rejection phenomena are predominantly, if not exclusively, lymphocytes and plasma cells.[2-6] Rejection of experimental penetrating (full thickness) corneal grafts may become evident first in the endothelial layer, in the epithelium, or in the whole graft at once.

The purpose of this paper is to report ultramicroscopic epithelial changes of corneal grafts during the rejection phenomena. Light microscopic alterations of the isolated epithelial layer have been previously described by others.[5]

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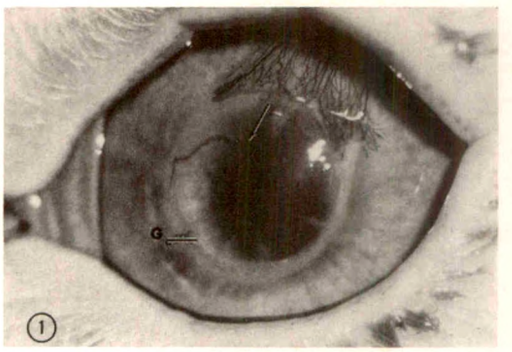



Fig. 1 (Kanai and Polack). Photograph of grafted eye showing rejection of graft epithelium. The methylene blue stained area (arrow) separated the host epithelium from the rejecting graft epithelium. Rejection moved in the direction indicated by the arrow. Beginning or endothelial-stromal rejection is present near the scar.

## MATERIALS AND METHODS

Adult albino rabbits (4 kg) were used throughout this experiment. Penetrating keratoplasties (5 mm) were performed between pairs of rabbits and, one week later, subcutaneous skin grafts (3 × 3 cm) were exchanged between the same pairs which exhibited clear corneal transplants.

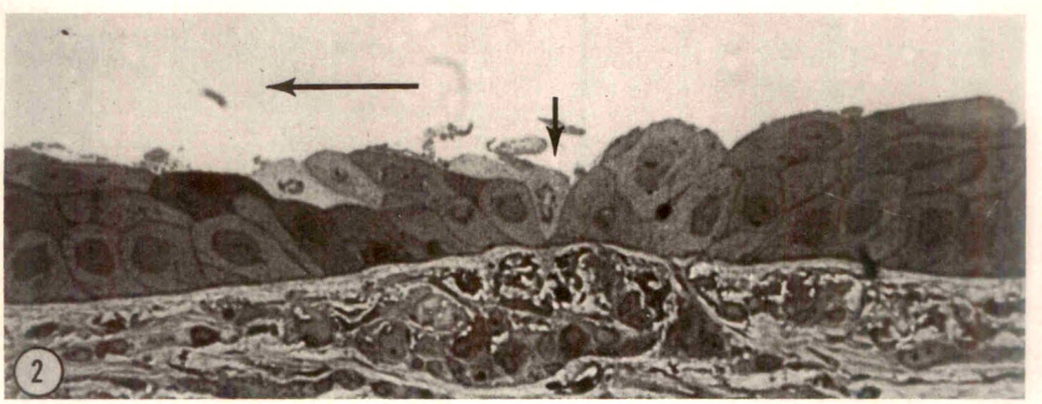



Fig. 2 (Kanai and Polack). Cross-section of epithelium in area of active rejection. Rejection line is indicated by the vertical arrow. Horizontal arrow shows direction of rejection. Note altered cell morphology, cell residues in superficial layers and leukocytes with epithelium. Some leukocytes and fibroblasts are present in subepithelial layer (toluidine blue, ×400).

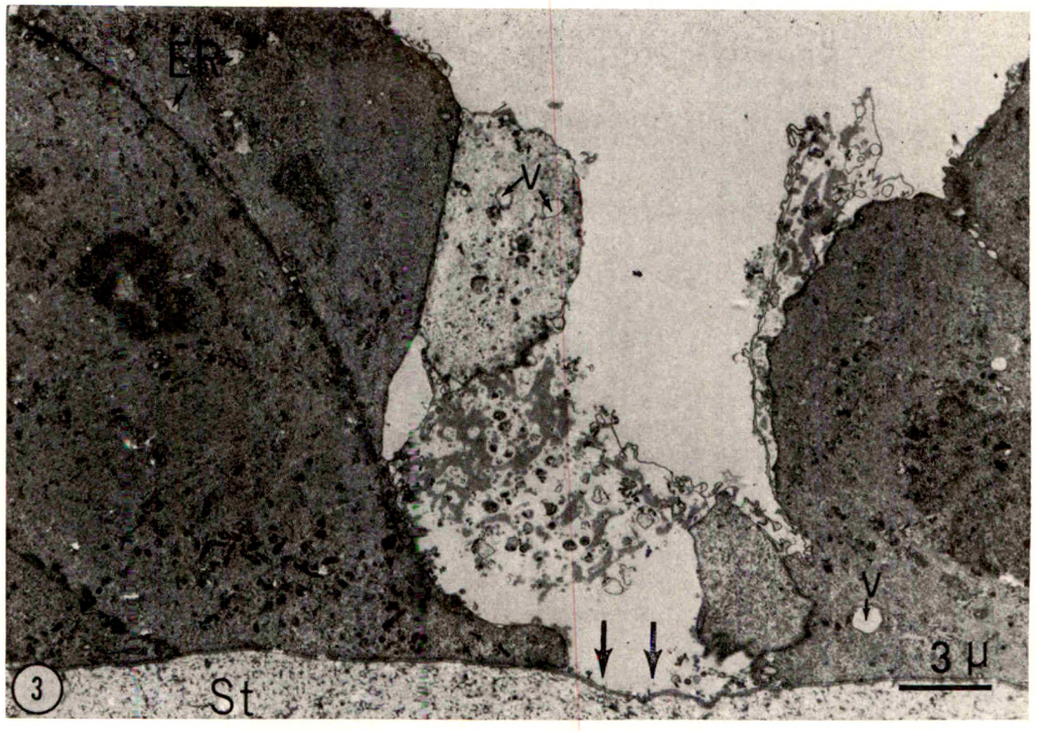



Fig. 3 (Kanai and Polack). Electron micrograph showing destroyed epithelial cells in area of rejection line. Cell residues and cell membranes remain (arrows). Remaining cells show dilated endoplasmic reticulum (ER) and vacuoles (V). Stroma (ST) (×4200).

Grafted eyes were frequently examined for evidence of epithelial rejection which, when present, appeared as a faint, hazy line that stained with topical methylene blue (1%). The stained line, or rejection line, always started at the edge of the graft and, in four to seven days, migrated across the transplant (Fig. 1). This defect was the only visible area of graft alteration in six eyes studied; two other rabbits also showed evidence of endothelial and stromal rejection at the time of enucleation.

Specimens for electron microscopy were obtained at the stage shown in Figure 1. The tissue was properly marked to identify host and donor epithelium on either side of the rejection line. With the animal under pentobarbital anesthesia, 1% osmium tetroxide was dropped onto the corneal epithelium and the eye was promptly enucleated. The cornea was excised and immersed in the osmium fixative for one hour. Subsequently, it was cut in smaller pieces under the dissecting microscope, care being taken not to damage the epithelium, and then again fixed for one hour.

Fixed corneas were dehydrated in alcohols of increasing concentrations and embedded in Epon. These sections were studied with a Hitachi-11 electron microscope. Thick sec-

»»→

Fig. 5 (Kanai and Polack). Low-power electron micrograph showing basal epithelial cells surrounded by lymphocytes (Lym). Note the lobulated epithelial nuclei (N). Mitochondria are distributed throughout the whole cytoplasm. The endoplasmic reticulum is scanty and located around the nucleus. Stroma (ST) (×7100).

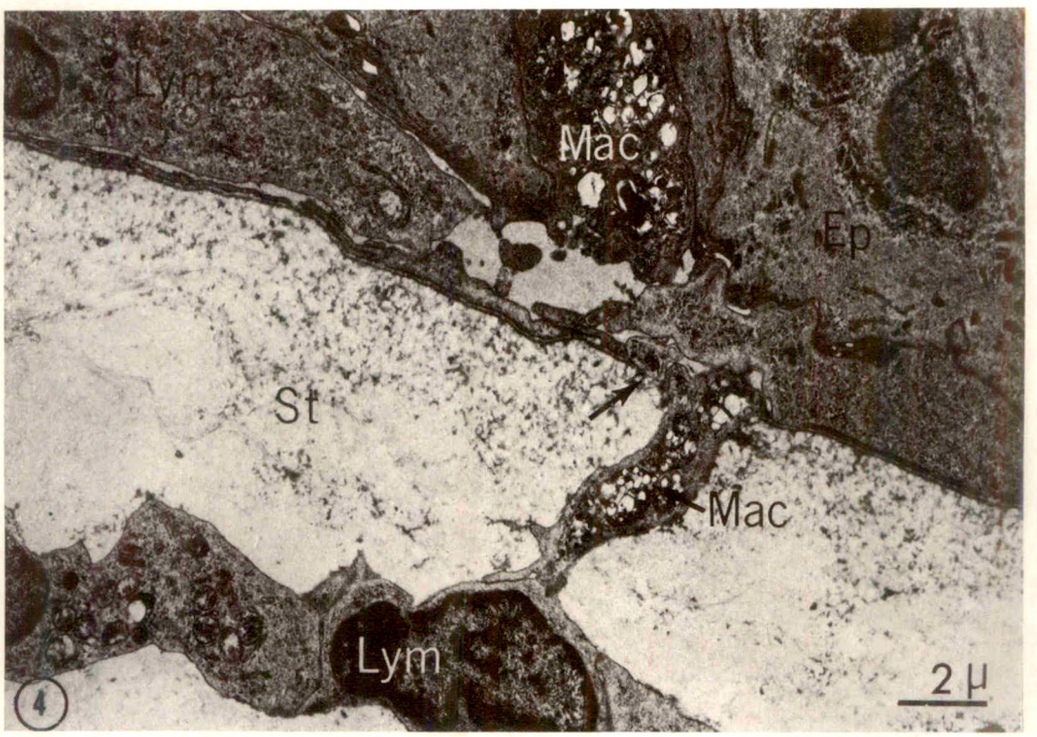
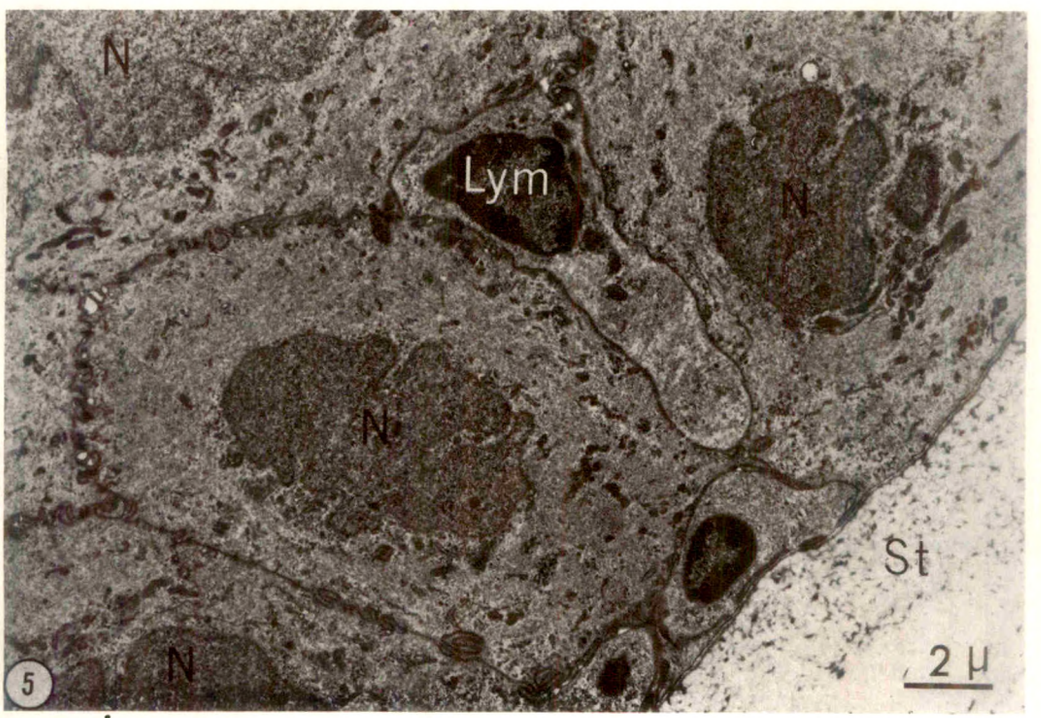



Fig. 4 (Kanai and Polack). Rupture of basement membrane (arrow) with penetration by a macrophage (MAC). A macrophage is also seen in the basal cell layer. Lymphocyte (Lym), epithelial cells (Ep), stroma (ST) (×6300).



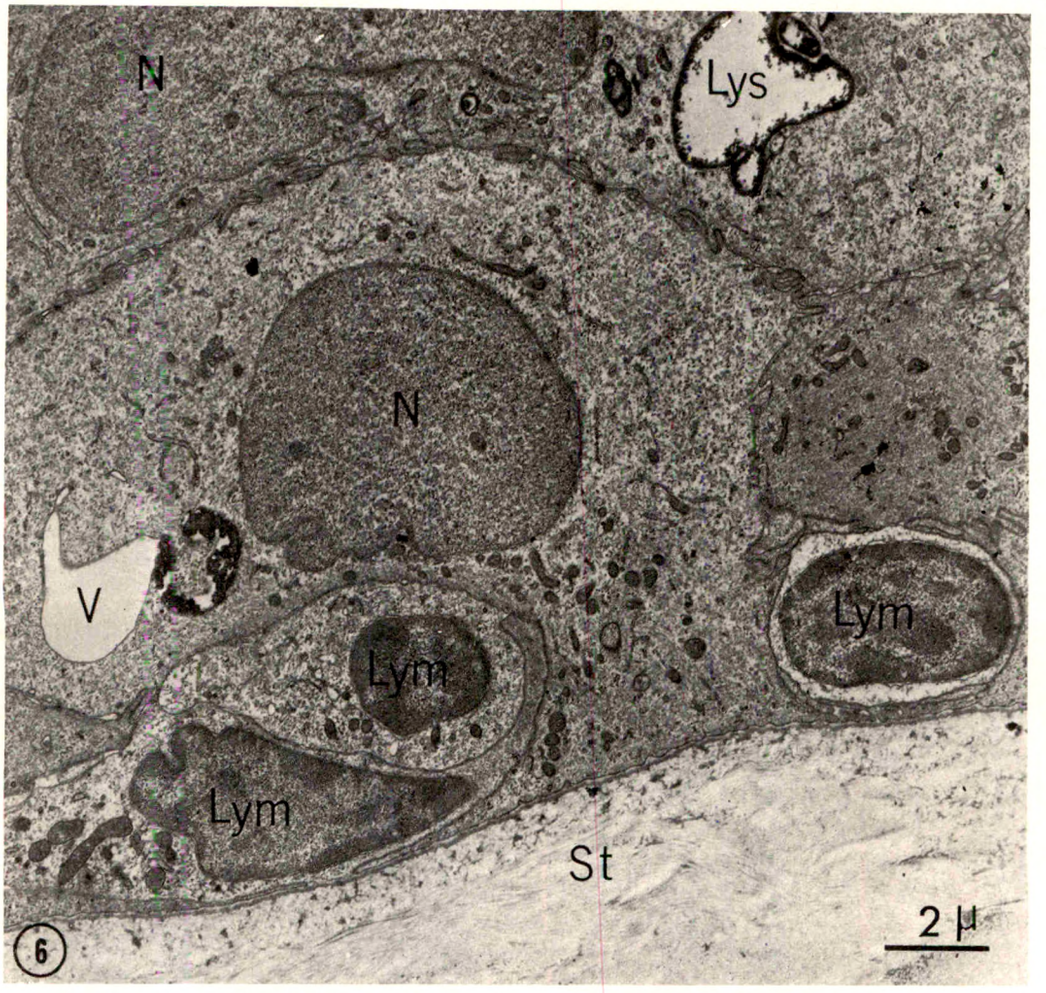



Fig. 6 (Kanai and Polack). Electron micrograph showing basal epithelial cells with lysosomes (Lys) and vacuoles (V) adjacent to lymphocytes (Lym). Note three different types of lymphocytes. Nucleus (N), stroma (ST) (×6000).

tions were stained with toluidine blue for light microscopy.

## Results

Light microscopic examination of thick (1 μ) sections showed epithelial cells on either side of the rejection line angled away from it (Fig. 2). Basal cells around the rejection line were flattened, rectangular, or triangular in shape. The rejecting cells stained weakly with toluidine blue, whereas the host cells or nonrejecting epithelial cells stained more intensely. In the center portion of the rejection line, epithelial cells demonstrated rupture of their plasma membranes and disorganization of their cytoplasmic structure. In some sections, only the remaining plasma membrane attached to the basement membrane could be observed (Fig. 3), while in others showing simultaneous stromal rejection, the epithelial basement membrane was fragmented and invaded by macrophages (Fig. 4).

Moderate distention of intercellular spaces were seen at all levels of the epithelium. The cytoplasmic (cellular) interdigitations were altered at the site of contact with lympho-

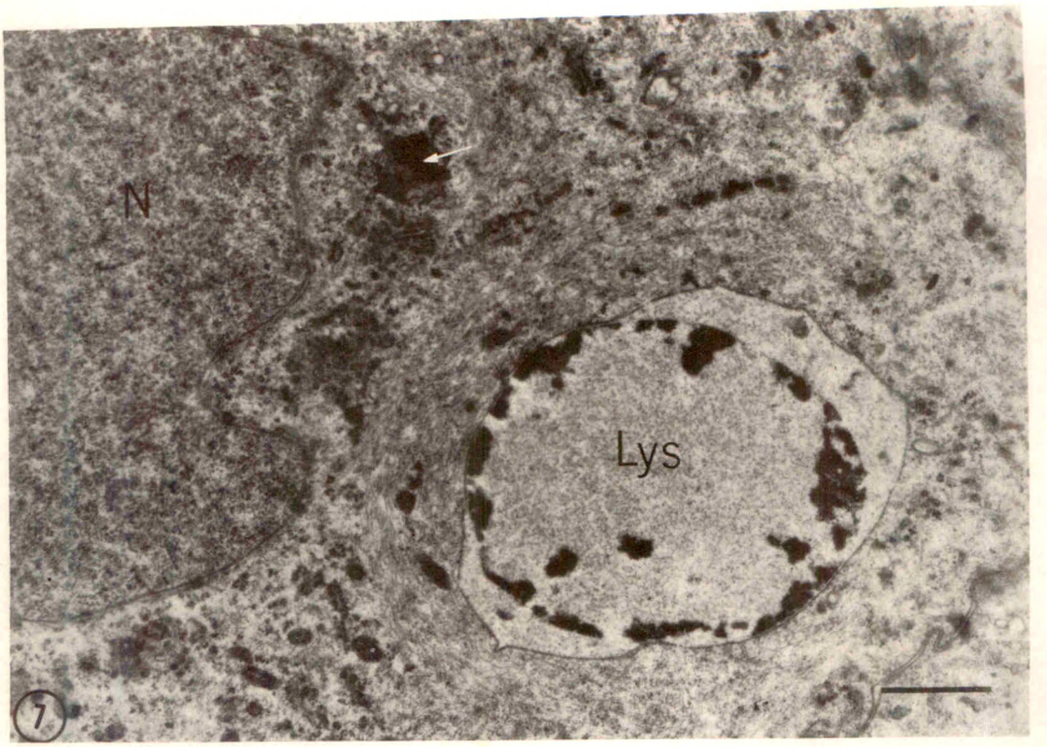



Fig. 7 (Kanai and Polack). Rejecting epithelial cell contains lysosomes (Lys) and a high density crystalline material (arrow). Nucleus (N) (×14700).

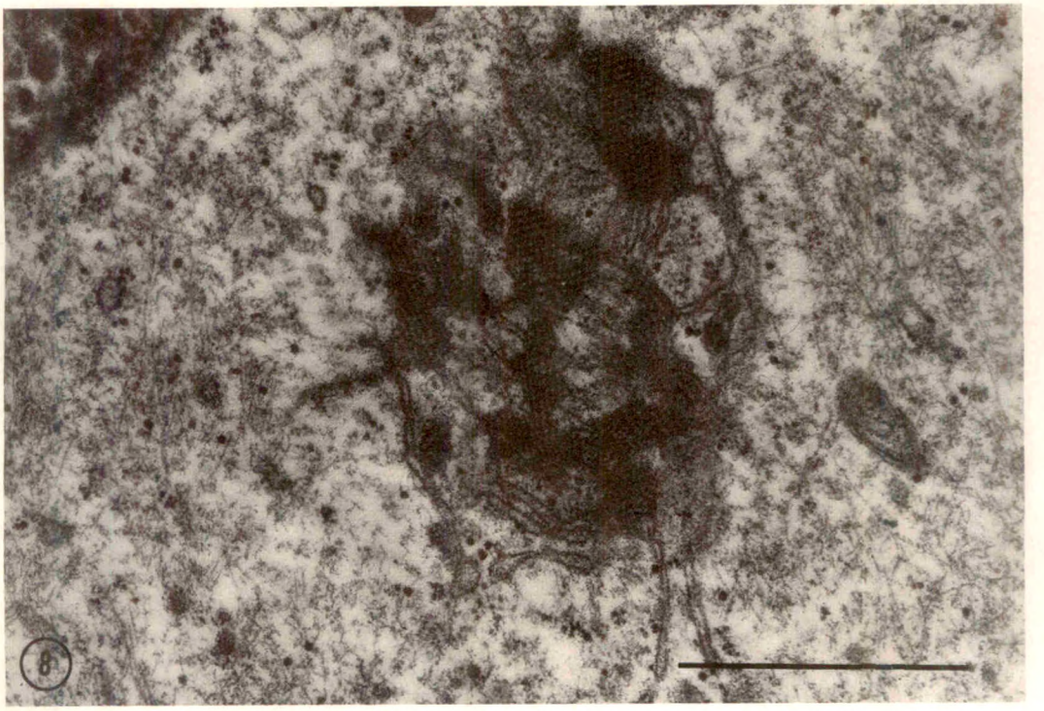



Fig. 8 (Kanai and Polack). High-power electron micrograph of high density material with crystalline structure shown in previous picture (×40,000).

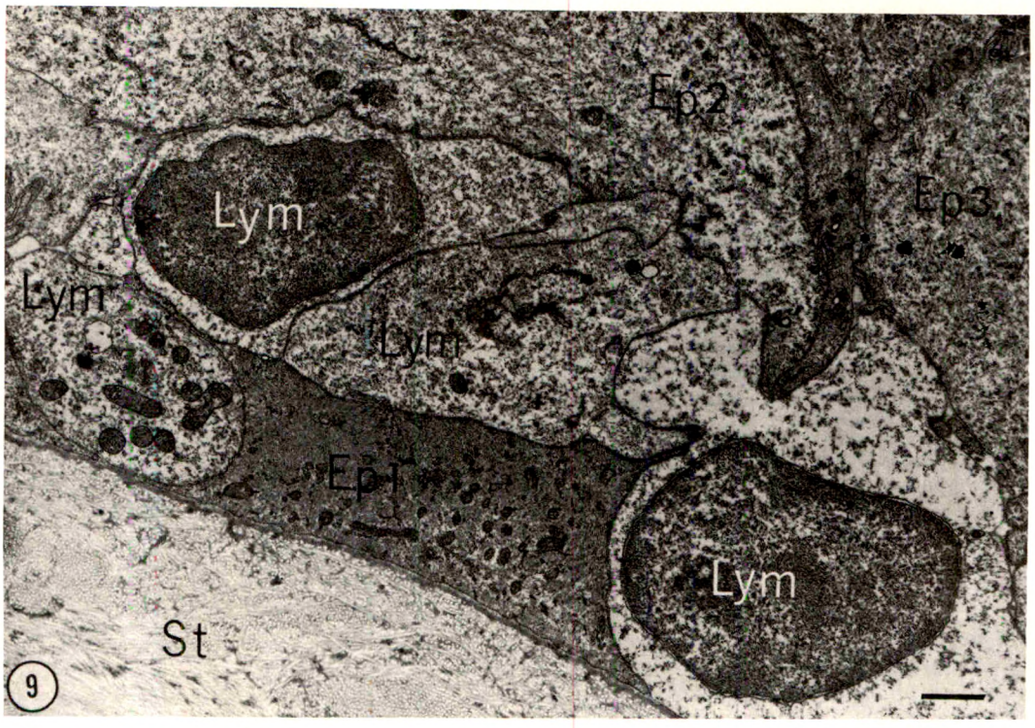



Fig. 9 (Kanai and Polack). Electron micrograph showing lymphocytes (Lym) and epithelial cells (Ep) of various densities. Lymphocyte on the right shows scanty RNP particles without other organelles. The cytoplasm of epithelial cell (Ep 1) is denser than that of other epithelial cells (Ep 2 and 3). Stroma (ST) (×8000).

cytes, resulting in a smooth cell boundary without desmosomes (Fig. 5).

Mitochondria were round or oval and evenly distributed throughout the cytoplasm. The endoplasmic reticulum was scanty, usually located around the nucleus, and occasionally showed moderate dilation. RNP particles (ribosomes) were observed around the nucleus or near the cell membrane; the Golgi complex located near the nucleus showed vesicles.

Several epithelial cells in contact with lymphocytes showed cytoplasmic vacuoles and lysosomes (Figs. 6 and 7). High-density crystalline substances without a limiting membrane were also seen in the cytoplasm and were located within the Golgi complex area (Figs. 7 and 8).

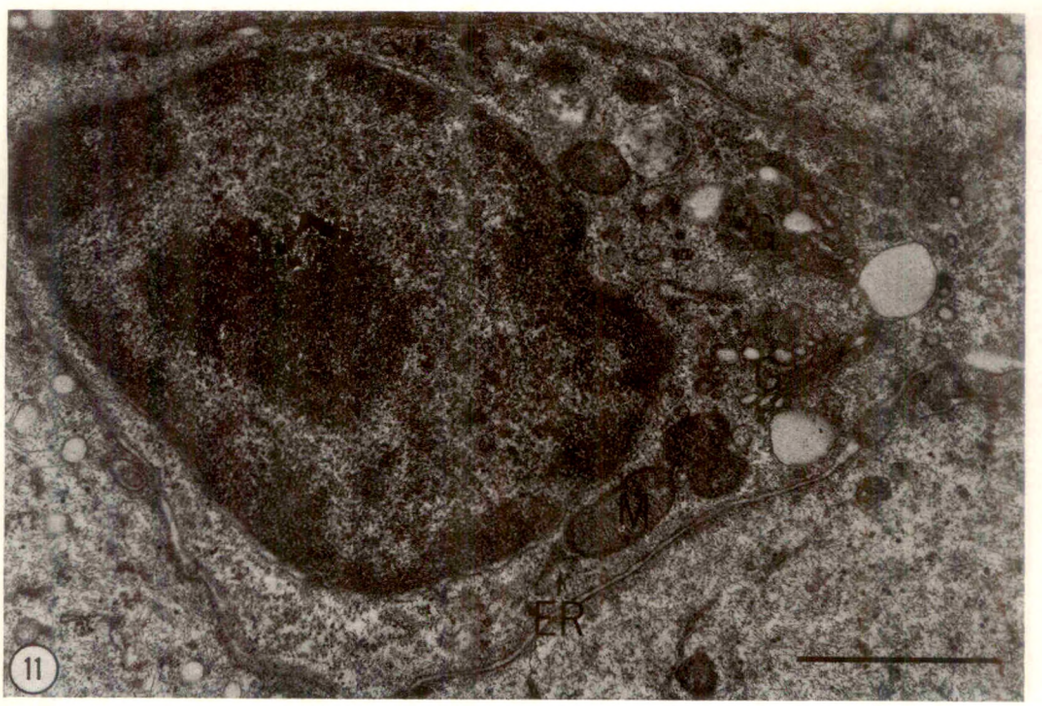
Lymphocytes were observed within the rejected epithelial cell layer (Fig. 9) or, at times, on the basement membrane; they were smaller than epithelial cells, round, oval, or pear-shaped, with round or oval nuclei and condensed chromatin (Figs. 5 and 10). Typical, small or middle-sized lymphocytes contained large mitochondria, sparse endoplasmic reticulum, a Golgi complex, and free RNP particles (Fig. 10). Others had few mitochondria, distended endoplasmic reticulum, vesicles or vacuoles in the area of the Golgi complex, and scanty scattered RNP particles (Figs. 9 and 11). No plasma cells



Fig. 11 (Kanai and Polack). Lymphocyte contains a distended endoplasmic reticulum (ER) and vesicles or vacuoles in the area of the Golgi complex (G). Mitochrondria (M) (×27,000).




Fig. 10 (Kanai and Polack). Electron micrograph shows three lymphocytes in the basal epithelial layer. Cell on left shows large mitochondria and well developed Golgi complex. Lymphocyte in the center shows distended endoplasmic reticulum (×8800).



were found in the area of rejecting epithelium.

## Comment

Our studies demonstrate epithelial cells of penetrating homografts undergoing rejection. Cell damage occurred in areas invaded by lymphocytes and was characterized by disorganization of their cytoplasm, changes in density, vacuolation, disappearance of organelles, and rupture and detachment of basal epithelial cells from the basement membrane. These alterations are similar to those described in electron microscopic studies of rejected endothelial cells of experimental homografts.[6] Morphologic changes in lymphocytes were also present, but these could not be related to the various stages of epithelial cell rejection with which they were associated.

The area of active rejection was confined to a band 80 to 100μ wide, seen as a line of haziness in the epithelium or staining with methylene blue. This line of rejecting cells was typified by its migratory character across the graft[5] in a similar fashion as endothelial-cell rejection advanced in rejecting homografts.[3]

Rejection of epithelium from a corneal graft may seem an unlikely phenomenon several weeks after transplantation, if one accepts the fact that corneal epithelial cells have a high turnover rate.[7] However, persistence of grafted epithelial cells for over two weeks was demonstrated by Khodadoust and Silverstein[5] in tritium-labeled donor corneas, and possibly for months by the method of rejection of lamellar grafts they described. The demonstration of a rejection phenomena with its characteristic clinical and histologic picture is good evidence that the cellular changes present are caused by an immunologic phenomena.

## Summary

Penetrating corneal allografts were performed in albino rabbits, and rejection was induced by a skin graft from the same donor; 12 to 14 days later, rejection of corneal graft epithelium developed. Electron microscopic studies showed epithelial cells with cytoplasmic changes, loss of organelles, vacuolation, and rupture of cell membrane. Lymphocytes of varied morphology were present in the area of cell rejection.

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# NEW PACHYMETER TO MEASURE CORNEAL THICKNESS

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Measurement of the corneal thickness is of clinical importance in several conditions, including keratoconus when periodic determinations of the apical thickness is a practical method of establishing the degree of thinning of the corneal tissues. In cases of corneal edema it serves to correlate the loss of vision and the edematous condition of the cornea. The thickness of the cornea should also be established in eyes affected with bullous keratopathy to determine if it exceeds 1.2 mm, in which case the prognosis is favorable for either a keratoplasty or a prosthokeratoplasty.

To this end, we have developed a new pachymeter* which makes possible the determination of the thickness of a clear cornea with an accuracy of within .02 mm. A totally opaque cornea cannot be measured.

The calibration of this new pachymeter is based on a refraction index of 1.376, the same as that of the normal cornea. This represents an entirely new approach. A search of the literature has revealed no other model of pachymeter calibrated on the normal corneal refraction index of 1.376.

Gunnar von Bahr,[1] basing his pachymeter on principles similar to those used by Blix to construct his ophthalmometer, mounted two planes of plate glass, one in front of the condensing lens and the other in front of the microscope of the slit lamp. When these plates were rotated, the reflection of the ray on the endothelium could be displaced and made to coincide with the reflection of the ray on the epithelium. The thickness of the cornea was calculated from the angle of revolution, the thickness and index of refraction of the glass plate and the corneal radius.

Maurice and Giardini[2] modified this method. They used a single one-fourth inch thick persplex plate in the illuminating beam from the slit lamp traversed by a horizontal cut covered by a thin strip of colored celluloid. Their apparatus can be adjusted so a white reflection from the posterior surface and a colored reflection from the anterior surface of the cornea are seen in the microscope at the same time. These reflections are aligned by rotating the persplex plate and the angle of rotation gives the corneal thickness.

In 1932, Goldman[3] described a new ocular to measure the transparent media of the anterior pole of the globe. It is mounted inside the right tube of the microscope of the old Haag-Streit slit lamp. The angle is formed by the beam of light set at 60° from the microscope and a system of gears is adapted to provide the reading.

## DESCRIPTION OF NEW PACHYMETER

Basically, the instrument consists of a double mirror (Fig. 1, see A and B). One mirror is movable, replacing the usual mirror in the Haag-Streit 900 slit lamp. Thus, separate images are obtained from the epithelial and endothelial surfaces. These surfaces can be measured separately by means of a calibrated gearing system.

The beam emitted by the slit lamp strikes the cornea surface (Fig. 2) at B and reaches C (the endothelial surface), which is viewed with the microscope through point A. The corneal thickness is determined when the beam from the upper slit lamp mirror strikes the corneal surface at point A (Fig. 2).

From the Edward S. Harkness Eye Institute of Presbyterian Hospital and the Department of Ophthalmology, Columbia University, College of Physicians and Surgeons, New York, New York. This investigation was made possible by Grant NB-04968-03 from the National Institutes of Health, Bethesda, Maryland, and by a Fight for Sight Grant-in-Aid from the National Council to Combat Blindness, Inc., New York, New York.

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* This instrument is manufactured by H & I Instrumentation, 293 Carlton Terrace, Teaneck, New Jersey 07666.

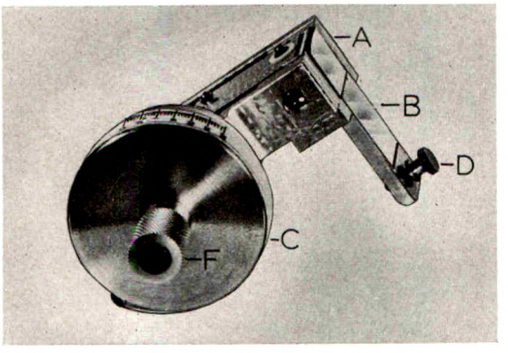



Fig 1 (Cardona and DeVoe). The instrument consists of two arms united at an angle of 90°. One side is the slide rest, which fits into the mirror housing of the lamp. This arm has two front surface mirrors, one fixed superiorly (A) and mounted on two crossed axes, and the other fixed inferiorly (B). The other arm is a 50 mm lever which multiplies the reading ×40. The calibrated dial (C) which synchronizes the two corneal images at "0" position adjustment is at one end. The fixation screw (D) fastens the pachymeter rigidly to the slit lamp.

A special method was used to calibrate this instrument. It eliminates the logarithmic error in calibration obtained with a plastic lens (1.495). The figure obtained with this calibration method very closely approximates the thickness of the human cornea.

When the corneal refraction index surpasses 1.376, a new calibration can easily be performed for research purposes by adjusting the refraction index of the variable thickness chamber to the value desired.

This calibration was chosen for practical purposes. A base curvature of 7.75 and a refraction index of 1.376 were selected as average values for the present calibration. The instrument was checked and the equivalent values are shown in Table 1.

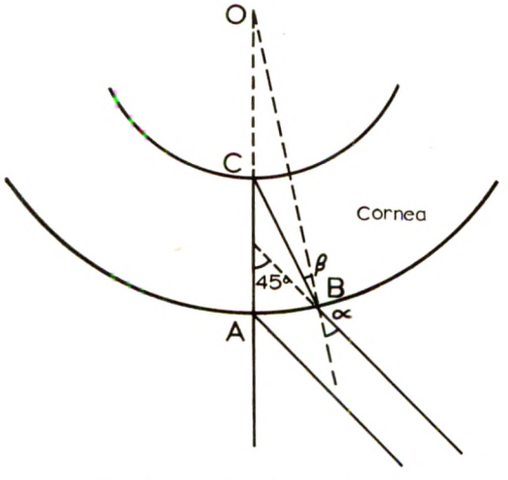



Fig. 2 (Cardona and DeVoe). Diagram showing the pattern of the beam and the physical bases used in corneal thickness determination. The formula is: A + (Cos − Sine) $n^2$ − $sine^2$ + (Cos + Sine) Sine.

### Measurement of corneal thickness

A total of 204 healthy corneas from 102 patients of different races, age, and sex were measured. Two zones were selected, the central and peripheral, because they afforded great precision. No appreciable changes were noted with varying refractive errors except two eyes with high myopia (−9.50 to 16.00). In these cases the central corneal thickness was 0.535 mm, or approximately .024 mm below our average finding of 0.651 mm. The average corneal thickness at the periphery was 0.745+ mm.

## Summary

A new simple instrument to measure the thickness of the cornea is designed for use with the Haag-Streit 900 slit lamp. Its calibration is entirely based on a chamber filled with a solution which has 1.376 index of refraction similar to the human cornea.

TABLE 1

EQUIVALENT VALUES (IN MM)

| Plexiglass Thickness in mm (N-1.49) | Human Cornea (N-1.375) | | Equivalent Thickness of Human Cornea |
|---|---|---|---|
| | Inside Radius | Outside Radius | |
| 0.25 | 8.00 | 8.25 | 0.22 |
| 0.50 | 7.75 | 8.25 | 0.45 |
| 0.75 | 7.50 | 8.25 | 0.68 |
| 1.00 | 7.25 | 8.25 | 0.90 |
| 1.25 | 7.00 | 8.25 | 1.13 |
| 1.50 | 6.75 | 8.25 | 1.35 |
| 1.75 | 6.50 | 8.25 | 1.58 |
| 2.00 | 6.25 | 8.25 | 1.80 |
| 2.25 | 6.00 | 8.25 | 2.03 |
| 2.50 | 5.75 | 8.25 | 2.25 |
| 2.75 | 5.50 | 8.25 | 2.48 |
| 3.00 | 5.25 | 8.25 | 2.70 |

This instrument is primarily used to study the thickness of the corneal before insertion of a keratoprosthesis. The corneas must measure at least 1 mm in thickness. If the cornea is thin, a graft is advisable in order to increase the amount of collagen support as a safety measure.

ACKNOWLEDGMENT

We thank Dr. S. Mishima who kindly reviewed the mathematical portions of this manuscript.

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# CONJUNCTIVAL AND CORNEAL CALCIFIC DEPOSITS IN UREMIC PATIENTS

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Deposition of calcium crystals in the limbus and conjunctiva of patients with otherwise normal eyes has long been recognized to occur with hypercalcemia.[1-3] Recently, however, conjunctival metastatic calcification has been reported in uremic patients with low or normal serum calcium.[4,5] It has been felt that the sine qua non for this phenomenon is an elevated serum calcium and phosphorus product, usually in the neighborhood of 70 mg%.[4,5]

The present study was undertaken to analyze further the calcium and phosphorus concentrations necessary to induce limbal and conjunctival calcification and to determine the effect of chronic hemodialysis on these deposits.

## MATERIALS AND METHODS

A total of 18 consecutive patients between the ages of 21 and 65 years, who were undergoing hemodialysis for periods of from two to 33 months, were studied. All had previously undergone extensive medical evaluation and laboratory testing in the Renal Service of the New York Medical College. Each patient was given a complete ocular examination, including visual acuity, refraction, biomicroscopy, applanation tonometry, and ophthalmoscopy. In addition, slit lamp photography of the conjunctiva and cornea was performed and repeated at periodic intervals.

From the Department of Ophthalmology and the Department of Medicine (Dr. Lonergan) of the New York Medical College. This study was supported by USPHS Grants NS-07162-04 and PH 43-67-654, by Grant 69-869 from the American Heart Association, and by Grant T-517 from the American Cancer Society, Inc.

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## RESULTS

The age and sex distributions of the 18 patients included in this study are found in Table 1, which also includes their diagnoses and known duration of disease.

Biomicroscopy was essential for the detection of the conjunctival microcrystals in all cases examined, but certain limbal deposits were grossly visible. All deposits were invariably located in the palpebral fissure. Conjunctival deposits were found immediately beneath the conjunctival epithelium, which was elevated over these areas. Small crystals tended to be white in color, but

TABLE 1

PATIENT DATA

| Patient No., Age and Sex | Diagnosis | Duration of Disease | Duration of Hemodialysis (months) |
|---|---|---|---|
| 1. 41-M | Malignant hypertension | 5 months | 3 |
| 2. 26-M | AGN | 5 months | 4 |
| 3. 65-M | Chronic pyelonephritis | 15 years | 18 |
| 4. 21-M | CGN* | 1 year | 6 |
| 5. 38-M | CGN | 2 years | 20 |
| 6. 50-M | CGN | 28 years | 7 |
| 7. 49-M | Polycystic disease | 3 years | 10 |
| 8. 25-M | CGN | 2 years | 6 |
| 9. 57-M | CGN | 6 months | 4 |
| 10. 27-M | CGN | 1 year | 9 |
| 11. 22-M | CGN | 16 years | 15 |
| 12. 21-M | CGN | 6 months | 2 |
| 13. 36-F | CGN | 3 years | 14 |
| 14. 35-F | CGN | 3 months | 2 |
| 15. 54-F | Renal failure | 2 months | 2 |
| 16. 41-F | CGN | 3 years | 8 |
| 17. 25-F | Polycystic disease | 3 years | 33 |
| 18. 32-F | Amyloidosis | 2 years | 6 |

* AGN = acute glomerulonephritis, CGN = chronic glomerulonephritis.

larger depositions were flat and colorless. The deposits were superficial to the episcleral vessels and did not move with blinking.

Most commonly, limbal calcification formed a half-moon-like arc concentric with the limbus. In all instances, these deposits extended from sclera onto cornea without an intervening area of clear cornea. Of the 18 patients studied, calcium crystals were present bilaterally at the corneoscleral limbus in nine patients and unilaterally in three. Conjunctival crystals were noted bilaterally in seven patients and unilaterally in three (Table 2). Four patients had solely conjunctival, and three solely limbal, calcification. In only two cases of this series were the "red eyes of renal failure" seen. In both of these patients, bacteriologic cultures were negative. Clinically, these patients manifested only conjunctival vascular congestion with mild chemosis. Follicles were not present, nor was there a significant degree of follicular hypertrophy of the tarsal conjunctiva.

The results of laboratory evaluations are listed in Table 3. From this data, it is apparent that serum calcium levels were low or normal in all patients having calcific deposits, whereas the phosphorus level was somewhat elevated to yield mean abnormal calcium-phosphorus products. However, no strict correlations were noted between calcium, phosphorus, or calcium-phosphorus products and the presence of calcific deposits in either the limbus or conjunctiva (Table 3). Furthermore, despite the fact that the calcium-phosphorus product was often reduced and held within normal range by

TABLE 2

DISTRIBUTION OF LIMBAL AND CONJUNCTIVAL CALCIFIC DEPOSITS IN 18 CONSECUTIVE UREMIC PATIENTS

| | Limbus | Conjunctiva |
|---|---|---|
| Bilateral | 9 | 7 |
| Unilateral | 3 | 3 |
| None | 6 | 8 |
| Total patients | 18 | 18 |
| Limbus and conjunctiva | 8 | |
| Limbus alone | 4 | |
| Conjunctiva alone | 3 | |
| Absent | 3 | |
| Total patients | 18 | |

TABLE 3

CHEMICAL VALUES OF PATIENTS IN THIS STUDY

| Patient No. | Crystals: Limbus RE | Crystals: Limbus LE | Crystals: Conjunctiva RE | Crystals: Conjunctiva LE | Serum Calcium (mg/100 ml) Norm = 9–11.5 | Serum Phosphorus (mg/100 ml) Norm = 3–4.5 | Serum Ca × P (mg/100 ml) Norm = 27–51.75 | BUN (mg/100 ml) Norm = 11–17 | Serum Creatinine (mg/100 ml) Norm = 0.6–1.3 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | − | − | + | − | 9.9 | 2.6 | 25.7 | 81 | 11.8 |
| 2 | + | ++ | − | ++ | 9.0 | 9.4 | 84.6 | 141 | 22.0 |
| 3 | ++ | − | + | + | 9.5 | 6.6 | 62.7 | 133 | 15.3 |
| 4 | − | − | + | + | 7.5 | 4.6 | 34.5 | 137 | 13.6 |
| 5 | ++ | − | − | + | 8.4 | 6.5 | 54.6 | 75 | 14.5 |
| 6* | ++ | ++ | ++ | ++ | 8.7 | 8.9 | 77.4 | 100 | 15.0 |
| 7 | + | + | +++ | +++ | 7.7 | 7.5 | 57.7 | 135 | 13.0 |
| 8 | + | + | − | − | 8.4 | 8.0 | 67.2 | 120 | 14.0 |
| 9 | − | + | − | − | 7.2 | 6.2 | 44.6 | 100 | 9.0 |
| 10 | + | + | − | − | 9.4 | 11.0 | 103.4 | 160 | 16.0 |
| 11 | + | + | − | − | 8.2 | 9.6 | 78.7 | 95 | 15.0 |
| 12 | + | + | ++ | ++ | 9.0 | 8.6 | 77.4 | 110 | 16.0 |
| 13 | − | − | − | + | 8.8 | 8.5 | 74.8 | 111 | 11.8 |
| 14 | − | − | − | − | 6.1 | 11.0 | 67.1 | 165 | 16.0 |
| 15 | − | − | − | − | 9.5 | 6.3 | 59.8 | 94 | 8.5 |
| 16 | − | − | − | − | 9.2 | 9.2 | 84.6 | 80 | 15.0 |
| 17 | + | + | ++ | ++ | 9.2 | 9.0 | 82.8 | 100 | 13.0 |
| 18* | ++ | ++ | ++ | ++ | 9.0 | 12.1 | 108.9 | 74 | 14.0— |
| Mean ± S.D. | | | | | 8.6 ± 1.0 | 8.1 ± 2.4 | 69.3 ± 21.5 | 109.7 ± 28.7 | 14.0 ± 2.9 |

* Indicates patients manifesting "red eyes" of renal failure.

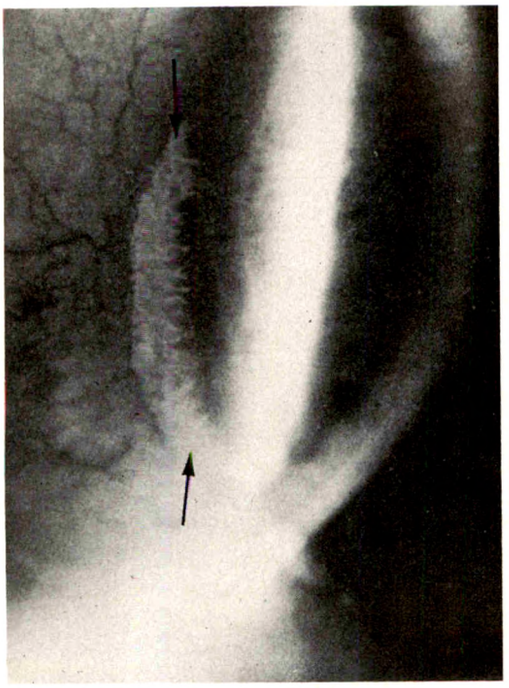


Fig. 1 (Harris and associates). Limbal calcific deposits in a 26-year-old man (Patient 2).

chronic hemodialysis, no change in the limbal or conjunctival calcification resulted during the one-year period of this study.

In both patients with "red eyes," rather heavy deposits were noted in both limbal and conjunctival locii (Table 3).

## Discussion

Limbal and conjunctival deposition of calcium salts is a frequent occurrence in advanced, acute and chronic renal failure.[1-5] Although there are exceptions, as shown in this study, the calcium-phosphorus product is usually in the neighborhood of 70 mg% in such patients. These findings are not usually noted with frequency in normal subjects or those in whom renal disease is less severe.[4,5]

Histologically, the site of this calcium deposition has been shown to be subepithelial and epithelial.[5] It is felt that these crystals consist of a calcium-phosphate salt, probably hydroxyapatite, as in crystals found in metastatic calcification in other locii.[5]

Limbal calcific deposits in these patients occasionally resembled Vogt's white limbus girdle (Fig. 1), but the limbus girdle is rarely seen in young patients and the deposits are usually not quite this large and coarse. The limbus girdle is most often yellowish-white, whereas the lesions described in the current study are chalk-white in appearance.[6]

Initially, Berlyne and Shaw[4,5] postulated that the "red eyes of renal failure" occurred in those patients with deposits consisting of small crystals. It was felt that in those patients who had a shorter duration of renal failure the crystal size was an important factor in determining the presence or absence of ocular irritation. In our study, however, "red eyes" were noted in two patients with rather dense, conjunctival and corneal deposits involving large crystals (Fig. 2).

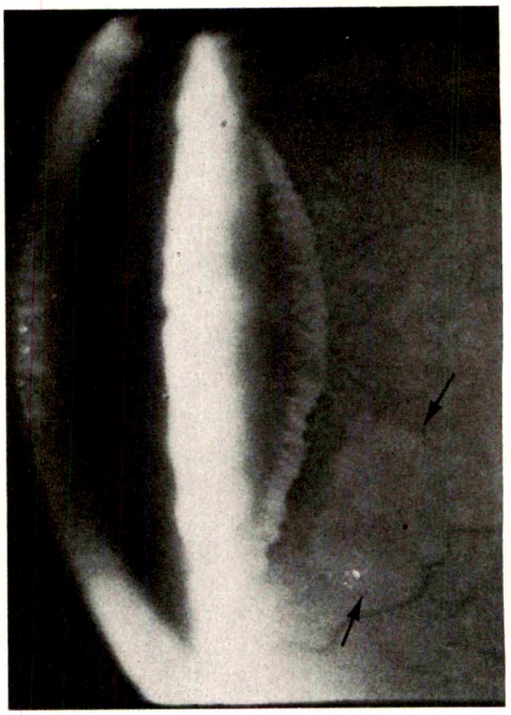


Fig. 2 (Harris and associates). A large, conjunctival, calcific deposit in a 50-year-old man (Patient 6). Extensive limbal crystalline material is also evident.

Moreover, the duration of disease in both of these patients was more than two years. These findings would tend to argue against crystal size as being an important determinant factor in the "red eye" syndrome.

Disappearance of ocular calcific deposits has recently been described to have occurred within several days of renal transplantation, despite persistence of elevated calcium-phosphorus products in some patients.[7] In the current study, calcific deposits were noted in patients undergoing routine, chronic hemodialysis for periods in excess of one year. No change could be detected resulting from or attributable to hemodialysis during this period.

The mechanism of deposition of calcium crystals remains unknown. It has been suggested in the past that the interpalpebral region is a site of crystal deposition in the presence of elevated calcium because of loss of carbon dioxide from the exposed conjunctiva. The decreased P $CO_2$ would be associated with a rise in pH, so that in the presence of an elevated calcium-phosphorus product, calcium-phosphate salts might precipitate.[1]

Fifteen of the 18 consecutive severely uremic patients in this series had biomicroscopically definable crystals. However, the three patients without calcific deposits had distinctly abnormal calcium-phosphorus products and were chemically as uremic as the remainder of the patients in this series who did have calcific deposits. Conversely, three patients with normal calcium-phosphorus products had minimal calcific deposits. It would appear that the ophthalmologist can use this observation to make the diagnosis of advanced renal failure in the overwhelming majority of cases.

## Summary

Examination of a consecutive group of 18 severely uremic patients disclosed an incidence of over 80% corneal or conjunctival calcific deposits, or both, in the presence of low or normal serum calcium levels. Serum phosphorus was elevated in all patients. The prerequisite for this phenomenon would appear to be an elevated serum calcium-phosphorus product in the neighborhood of 70. However, the three patients in this study who had no deposits were in no way distinguishable from other patients in this series with calcific findings on the basis of blood chemistry values or duration of disease.

The vast majority of these patients were asymptomatic and unaware of the calcific deposits. Limbal calcifications in uremic patients are distinguishable from Vogt's white limbus girdle by their presence in young patients and by the considerably larger and coarser crystal size, as well as the absence of a clear area of cornea at the limbus. Chronic hemodialysis appeared to have no influence on the distribution, size, or appearance of these crystals.

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# CRYOTHERAPY OF STROMAL HERPES SIMPLEX KERATITIS IN RABBITS

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In 1965, Krwawicz[1] found cryotherapy to be of benefit in the treatment of epithelial and stromal herpes simplex keratitis in humans. Corwin and associates[2] found cryotherapy of superficial herpes simplex keratitis in rabbits to be of little value. It is well known that virologists have used freezing as a means of preserving viruses.[3] However, there are conditions under which the herpes virus is adversely affected by freezing.[4]

Since application of cold to the cornea produced little or no damage to that structure, it was felt that experimental studies of cryotherapy on stromal herpes might be of interest.

## METHOD

Both eyes of adult New Zealand White rabbits were given 5 mg of prednisone subconjunctivally one day prior to virus inoculation. On the day of inoculation, after topical anesthesia (proparacaine HCl), the center of each cornea received 10 horizontal and 10 vertical scratches with an edge of a Lindner spatula. An attempt was made to make the scratches only through the epithelium. Three drops of PH strain of herpes simplex virus passed in mouse brain with an $LD_{50}$ of $10^{-5}/0.03$ ml were placed onto each cornea. Every rabbit eye thus treated showed a keratitis the next day.

Fourteen days following virus inoculation, all eyes showed a disciform keratitis. Though not all rabbits showed exactly similar lesions, there was a remarkable similarity

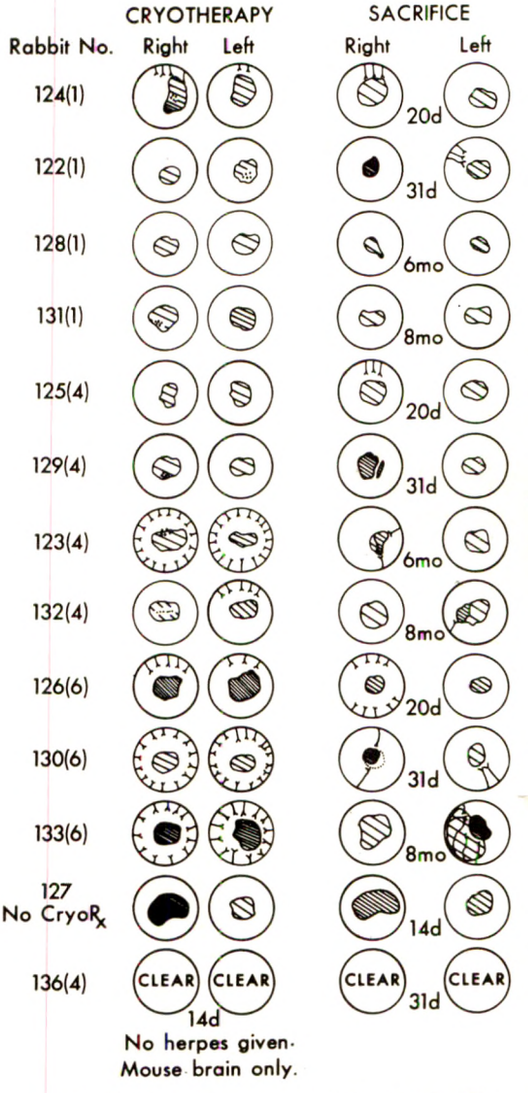



Fig. 1 (D'Alena, Okumoto, and Crawford). Clinical appearance of eyes in rabbits. Days (d) indicated are those after herpes inoculation. Numbers in parenthesis show the number of times the cryoprobe was applied to the right eye. The density of the crosshatching indicates the density of the cornea lesion. Stippling indicates fluorescein staining of the cornea. The Y-shaped areas show the extent of the corneal vascularization.

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in the extent of the keratitis in each eye of the same rabbit. At that time, the right eye of each rabbit was arbitrarily selected for cryotherapy, the left eye serving as control. Four identical cryoapplicators were made from a solid copper bar, tapered to a cone with a 3 mm ball on its tip. A tapered handle was made of polyethylene. A test tube containing the probe was placed in a small thermos of liquid nitrogen for at least five minutes. This allowed the temperature of the probes to be about −80°C. Each of the four probes was similarly treated and used in rotation, so that each probe attained about the

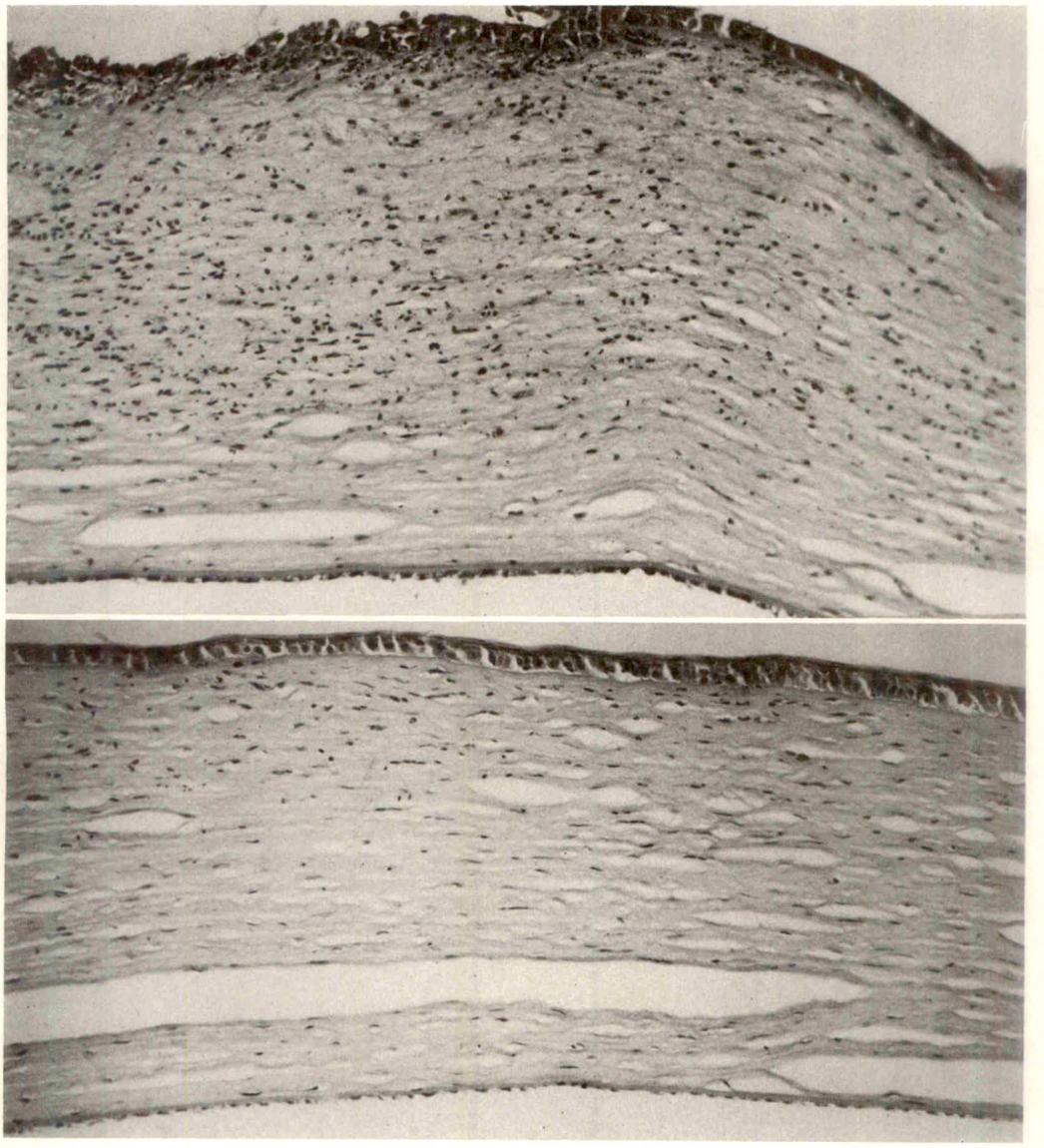


Fig. 2 (D'Alena, Okumoto, and Crawford). Rabbit No. 127. The right (top) and left (bottom) corneas 14 days following herpes inoculation. At this time the right eye would have been treated with the cryoprobe. Variability between the two eyes is evident. This rabbit showed the greatest variability between the two eyes of any rabbit in the series (hematoxylin and eosin, ×100).

same temperature. On the day of cryotherapy, each rabbit eyelid was swabbed with a moist cotton applicator and the material streaked on sheep blood agar before application of the probes.

The rabbits were divided into three groups. Group A had the cryoapplicator applied to the center of the right cornea for five seconds only. This application was sufficient to produce an obvious ice ball within the cornea. Group B had four applications of five seconds duration. Group C had six applications of five seconds' duration. The multiple applications were applied in a circle, overlapping the center of the cornea. There were five rabbits in each group except the last where there were four. One rabbit of each group was treated with mouse brain suspension alone, instead of herpes virus, and then received cryotherapy.

The eyes were examined with slit lamp and then photographed when indicated. The clinical severity of the disease was judged on the basis of evidence of pannus, exudate,

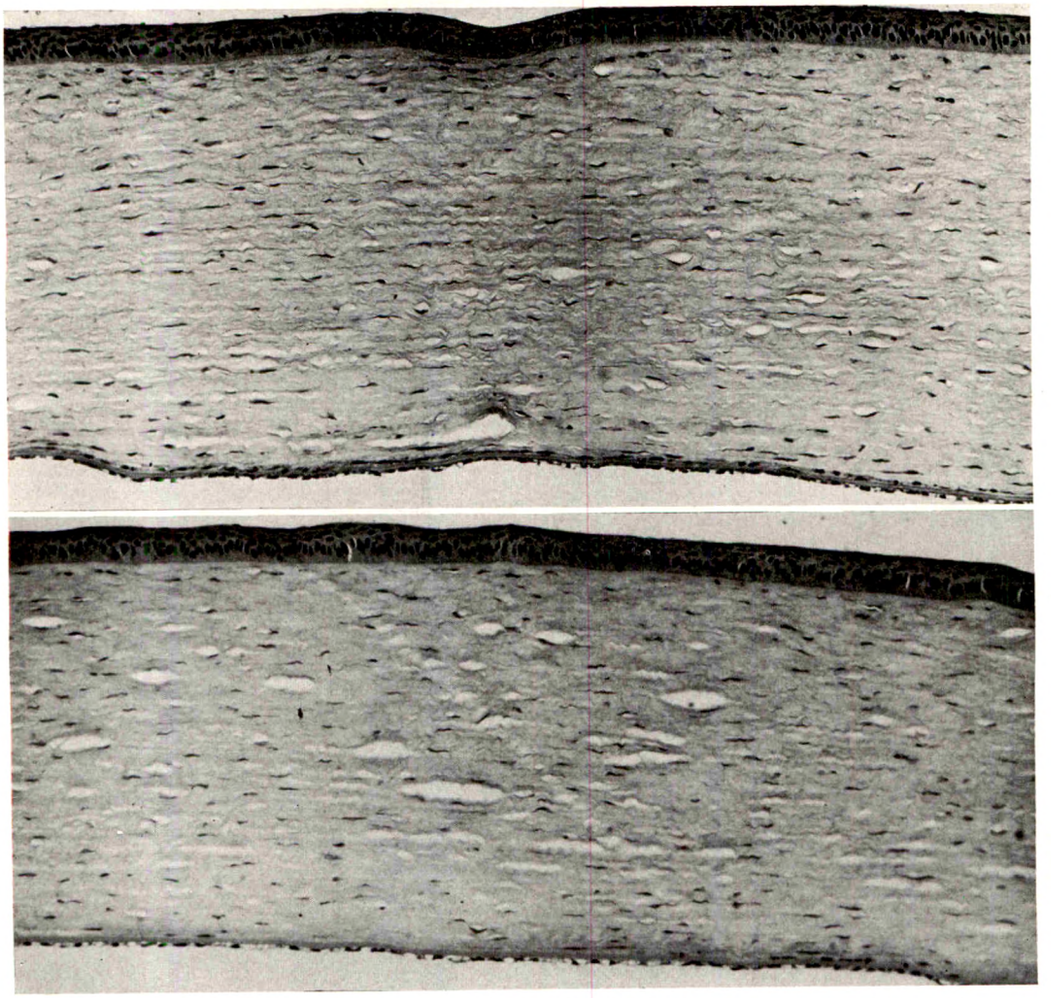


Fig. 3 (D'Alena, Okumoto, and Crawford). Rabbit No. 136. This rabbit was inoculated with mouse brain suspension alone, instead of herpes virus. The right eye (top) was then treated with four applications of cryotherapy. The rabbit was sacrificed 31 days following inoculation (17 days after cryotherapy). Essentially no difference between the right (top) and left (bottom) corneas is evident (hematoxylin and eosin, ×100).

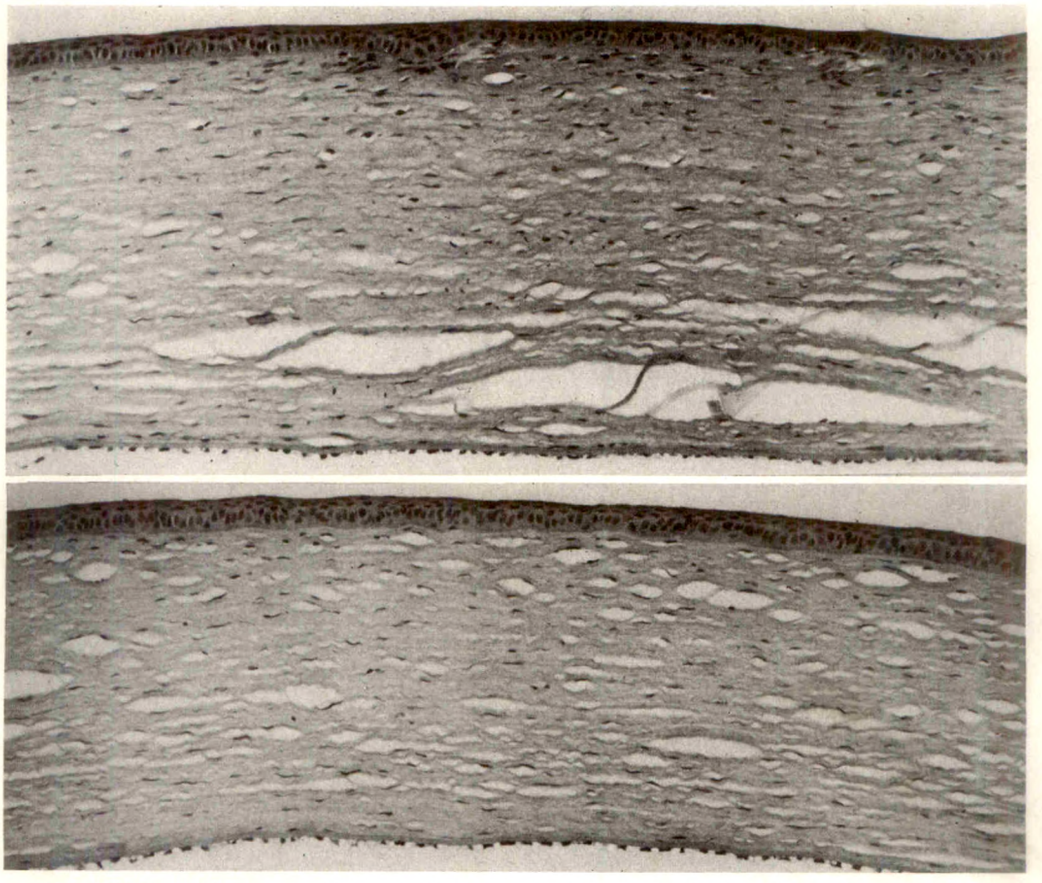


Fig. 4 (D'Alena, Okumoto, and Crawford). Rabbit No. 129. Right (top) and left (bottom) corneas of a rabbit sacrificed 31 days after herpes inoculation (17 days after four applications of cryotherapy of the right eye). Focal epithelial hyperplasia and more stromal inflammation is seen in the right cornea than in the left (hematoxylin and eosin, ×100).

corneal staining with fluorescein, extent of corneal edema, iris congestion, and presence of cells and flare as seen by the slit lamp. The animals were sacrificed at various intervals up to eight months following herpes inoculation at which time the eyes were sectioned and stained with hematoxylin and eosin.

## Results

The clinical findings showed that cryotherapy did not alter the course of the disease. In the treated eye of one rabbit that received four applications, two small superficial lenticular opacities were noted three weeks following cryotherapy. These opacities later became subepithelial and persisted until the rabbit was sacrificed seven and one-half months following cryotherapy (eight months after herpes inoculation).

In some rabbits, one eye was worse than the other prior to the cryogenic treatment. These differences were considered when the histological sections were reviewed and the clinical results evaluated.

Figure 1 summarizes the clinical results of the study. Cryotherapy produced a minimal amount of cells and flare in the anterior chamber even though the iris became moderately injected. From Figure 1 it is seen that six of 11 treated eyes were worse than its control eye; three eyes appeared better than

TABLE 1

SUMMARY OF HISTOLOGIC FINDINGS

| Rabbit No. | Rabbit Eye | |
|---|---|---|
| | Right | Left |
| 124 | 2 (iritis) | 1 |
| 122 | 2 | 4 |
| 128 | 1 | 1 |
| 131 | 1 | 1 |
| 125 | 2 | 1 |
| 129 | 2 | 1 |
| 123 | 3 | 2 |
| 132 | 1 | 2 |
| 126 | 2 | 4 (cyclitis) |
| 130 | 4 | 3 |
| 133 | 1 | 2 |
| 127 | 4 | 3 |
| 136 | 0 | 0 |

the control, and two pairs of eyes appeared approximately equal in the extent of corneal changes. Rabbit No. 127 was sacrificed 14 days following herpes inoculation, the day on which treatment was given to the rabbits (Fig. 2).

The rabbits that were inoculated with mouse brain suspension alone, showed no corneal lesions two weeks after cryotherapy. Rabbit No. 136 (Fig. 3) was treated in this manner.

Figure 4 (rabbit No. 129) shows the results of a rabbit treated with cryotherapy.

The histologic findings confirmed in general the clinical results.

Table 1 summarizes the histologic results of the study. The slides were read by one of us (B.C.) without knowledge of the clinical results. The eyes were grade 0 to 4 depending on the amount of inflammatory cellular reaction, vascularization, and scarring.

## CONCLUSIONS

Except for slight variations, cryotherapy, performed by the method outlined for this experiment, did not alter the course of stromal herpes simplex keratitis in the rabbit.

## SUMMARY

Both eyes of adult rabbits were given 5 mg of prednisone subconjunctivally one day prior to inoculation of the eyes with PH strain of herpes simplex. Fourteen days following virus inoculation, all eyes showed a disciform keratitis. At this time, the right eye was treated with a cryoprobe at a temperature of about −80°C. Three different intensities of freezing were used. Except for slight variations, cryogenics did not alter the course of experimental stromal herpes simplex keratitis followed over an eight-month period.

## ACKNOWLEDGMENT

The cryoprobes used in this study were designed and manufactured under the supervision of George Hilton, M.D.

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# MENISCUS-INDUCED THINNING OF TEAR FILMS

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Although studies of the physical chemistry of the tear film have emphasized its importance and characteristics,[1-9] much remains to be clarified, and little clinical application of this knowledge has yet been made. The purpose of this report is (1) to describe some in vitro phenomena of fluid films in the region of the menisci; (2) to show clinical examples of these in the tear film of normal and diseased eyes, and (3) to discuss the implications of these phenomena in tear film renewal.

## MATERIALS AND METHODS

Measured volumes of fluid (water, sodium fluorescein aqueous solutions, or milk) were placed on a glass surface which had been cleaned with a detergent solution and rinsed off with distilled water. After the fluid stopped flowing, the thickness of the fluid layer was measured by dusting talc on the surface and measuring the height above the surface under a microscope. The curvature of the edge was optically analyzed by noting the direction of a reflected beam of light from the surface, when a small light was moved above the edge. The direction of a beam that was refracted by the fluid before and after reflection at the glass surface was also studied.

The menisci raised by various wetted substances (paper clip, wire, dry spaghetti, toothpick, coins, contact lenses, etc.) were similarly analyzed by microscopic measurements and observation of the reflected and refracted beams of light.

The fluids were made to cover a larger area by gravity (tilting the glass) or by mechanically spreading the surface with any wettable object (glass slide, etc.). Measurements and optical studies were made of the spread film. Menisci in these stretched films were studied microscopically and optically, and profile curvatures were made of the menisci and the adjacent thinned area of the film. Optical sections of these surface curves were made with a slit lamp and photographed. Interaction of menisci of different height and curvature were studied. Movies and still photographs were made to document these phenomena in vitro and also in rabbit and human eyes.

## LABORATORY RESULTS

When 1 ml of water, milk or aqueous sodium fluorescein was placed on a horizontal glass surface, it spread so that its depth was between about 1.0 and 1.8 mm and its area was about 10 to 5.5 $cm^2$. If the fluids were set on the glass forceably, the area covered was greater and the depth comparably reduced.

At the edge of the fluid, reflections from a point source of hand-held light moved in the same direction ("with" movement) but more slowly, indicating the virtual image from a convex mirror surface. When starting with the image near the center of the fluid and moving the light towards the edge, the virtual image began to slow down almost a full centimeter from the edge, indicating the beginning of the convex curvature, even at this great distance from the edge (Fig. 1). The slowing of this virtual image became more noticeable on approaching the edge, indicating an increasingly stronger convex mirror toward the edge.

Transmitted light passing through a solution of fluorescein and reflected off the glass

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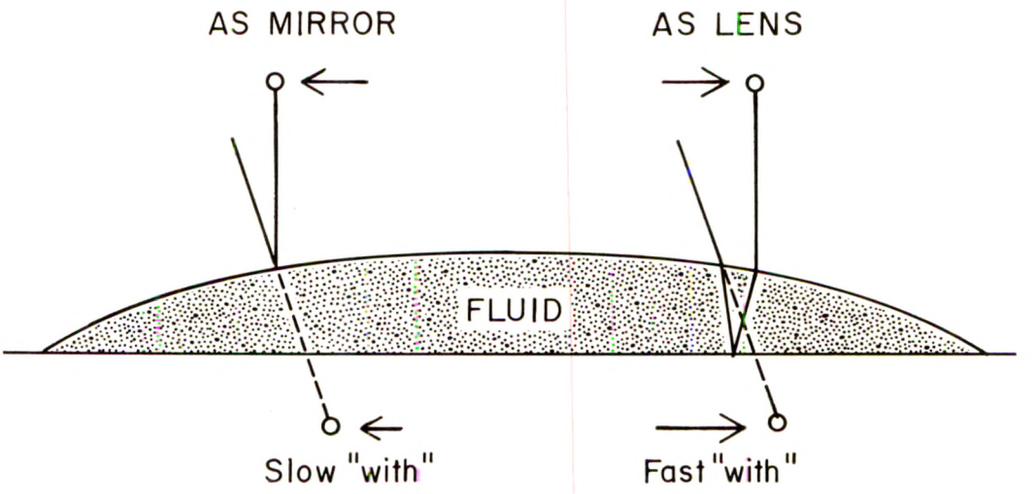



Fig. 1 (McDonald and Brubaker). Curvature analysis by moving a light above a solution of sodium fluorescein. The fluid acts as a convex mirror and reflects a slow "with" movement. It acts as a lens and transmits the greenish refracted ray to give a fast "with" movement.

looks green in contrast to the white color of the surface reflections. At the edge of the fluid the curved fluid lens forms a real image in air and therefore gives an "against" movement. Moving from the center, the transmitted green light starts to speed up

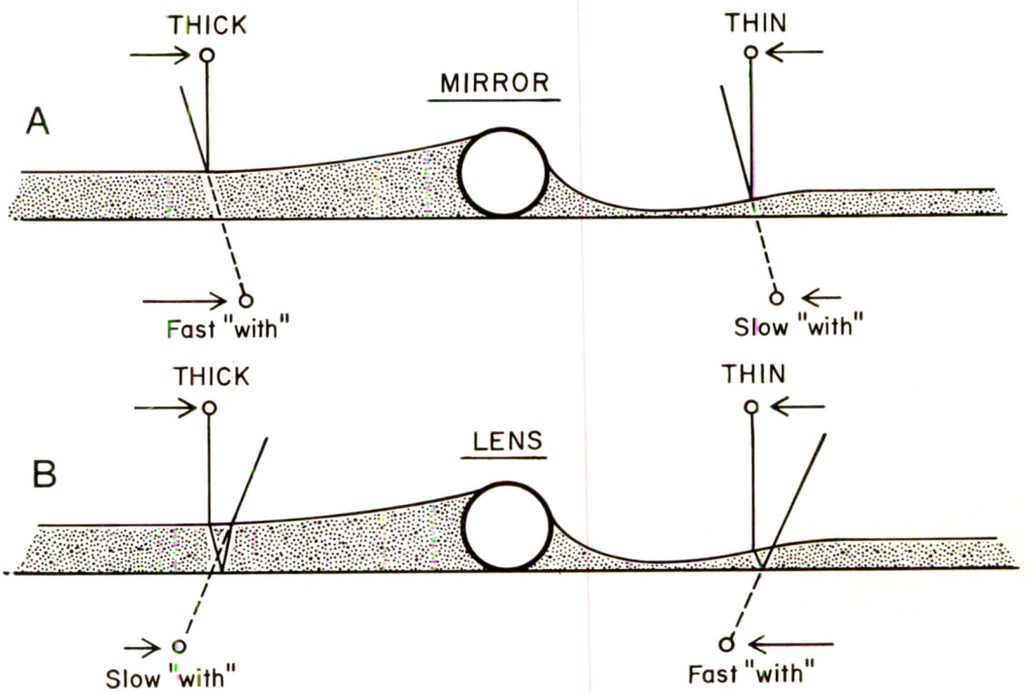



Fig. 2 (McDonald and Brubaker). Optical studies on thick films on the left show a rising surface by both the reflected and the refracted rays. Thin films on the right indicate an initial depression of the surface before rising into the meniscus.

("with" movement) as the gently curved surface acts first as a weak magnifying glass giving a virtual image behind the glass. As the curvature increases toward the edge, the image is converted to a real image in the air in front of the surface and has an "against" movement. The separation of the white reflected ray from the green transmitted ray at a point about 1 cm from the edge gives a sensitive means of detecting and analyzing variations in surface curvature.

Menisci raised from the surface of these relatively thick bodies of fluid lend themselves to study in a similar manner. As the light in front of the surface mirror is moved toward a meniscus, its virtual image begins to speed up in a "with" direction (Fig. 2, top left) at less than a centimeter away from the apex, and then as the light is continued in the same direction, the image converts into a real image with an "against" movement, as the surface mirror becomes more strongly concave. The transmitted ray, acting as a negative fluid lens, slows down in a "with" direction (Fig. 2, bottom left). The slowing increases as the apex is approached.

These studies indicate that the meniscus in a thick film (including the meniscus formed by bodies floating on deep volumes of fluid) gradually rises from the surface with the curvature gradually increasing in amount as the apex is reached. There is apparently no initial depression in the surface before the meniscus rises.

When such volumes of fluid were made to cover an area on the glass that was four to

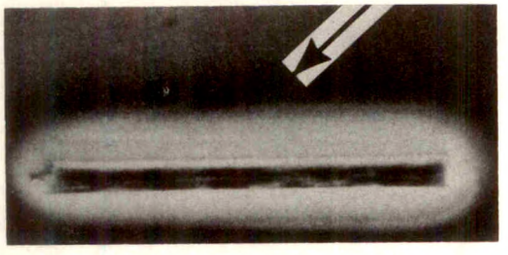


Fig. 3 (McDonald and Brubaker). Piece of uncooked spaghetti in a thin film of milk raises a meniscus which is surrounded by an area of thinning (arrow).

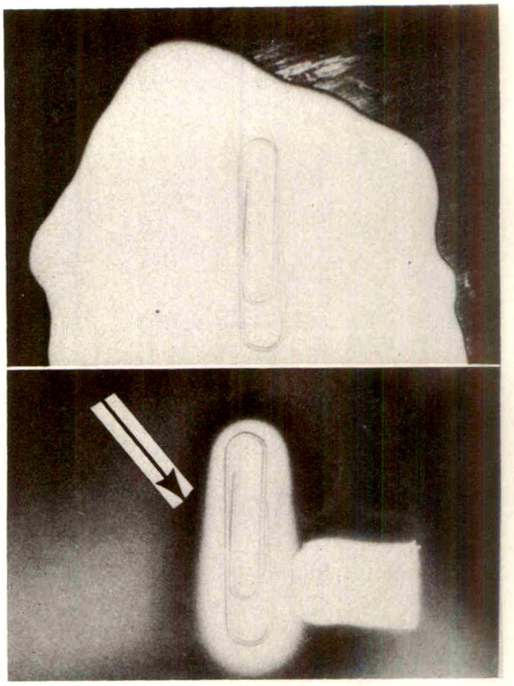


Fig. 4 (McDonald and Brubaker). Top: Paper clip in a thick film of milk shows no meniscus-induced thinning. Bottom: When glass is tilted to make the film thinner, a meniscus-induced thinning occurs. The white rectangular area is the light reflex.

10 times or more than the original area (and the film thickness then measured was 0.1 mm. or less) they acted differently. In these cases the meniscus that was formed was always surrounded by an area of thinning (Fig. 3). This could be seen grossly, but was made more noticeable when milk was put on dark glass, or when a solution of fluorescein was examined under ultraviolet light. This meniscus-related area of thinning could be made to disappear by fluid flow in from the side, provided that the fluid film was made deep enough to permit easy flow of fluid in from the edge. If the meniscus-induced thinning was not present, it could be induced by tilting the glass to make the film even thinner by gravity, or by spreading the film out to a greater area (Fig. 4). For example, no meniscus-induced thinning was noted at about 125μ but it was present when film thick-

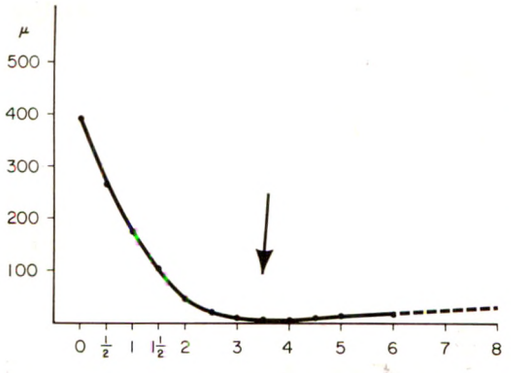



Fig. 5 (McDonald and Brubaker). Results of measuring the film thinning through a microscope. Abscissa is in mm.

ness was reduced to 110μ and was very prominent at 75μ.

Thinning of the film adjacent to the meniscus was confirmed by optical behavior or reflected and transmitted rays. As one approached the region of the meniscus, the reflected ray first showed a retarding "with" motion (Fig. 2, top right), and the transmitted refracted ray showed an advancing "with" motion (Fig. 2, bottom right). These findings confirm an initial depression in the surface in a concave manner before the meniscus rises above the surface toward its apex. Microscopic measurements (Fig. 5) and photographs confirmed the presence of this thinning of the film in the region of the meniscus.

Movement of the object causing the meniscus also moved the meniscus with its thinned area. This thinned region remained thin, unless the object was moved into a relatively deep part of the fluid. Microscopic examination of the thinned area in milk showed the rapid movement of globules of milk from outside of the meniscus through the thinned area into the meniscus. When two menisci of different size touched each other, they tended to become the same size (Fig. 6). The meniscus with less fluid would take from that of more fluid until they were in equilibrium.

The area of thinning adjacent to the meniscus was regularly the site of film fracture. Whenever the stretched film fractured, it almost invariably fractured first in this thinned region, followed by retraction of the film along the line of thinning. It was obvious that the film was weakest in the thinned part.

The intensity of the meniscus-induced thinning depended on the thickness of the surrounding film. If the thinned area could be easily filled in by laminar flow, as in a thick film, the thinned area disappeared by this mechanism. If the surrounding laminar flow was impeded by viscosity or thinness of the adjacent film, the thinned area maintained itself, and then frequently fractured there.

## Clinical observations

Both human and rabbit eyes regularly showed the same phenomena in the precor-

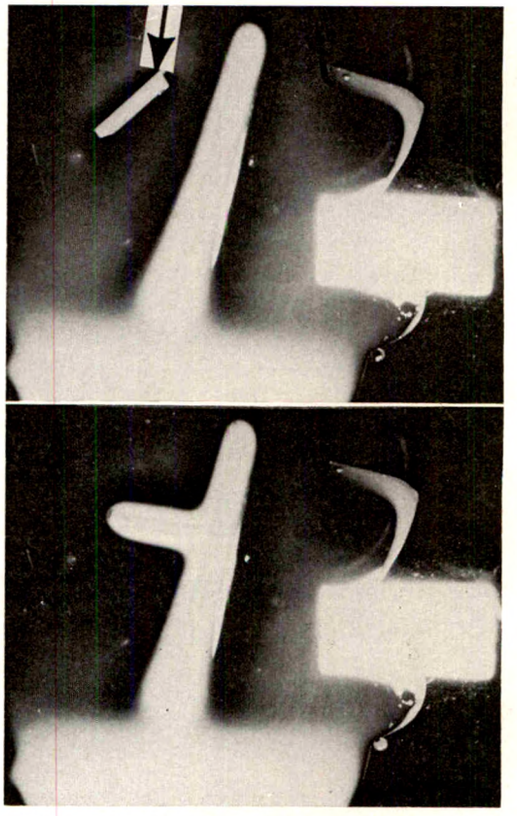


Fig. 6 (McDonald and Brubaker). Uncooked spaghetti in milk film which is stretched by gravity. Top: Meniscus of smaller piece (arrow) is small, acutely curved, and "thirsty." Bottom: Menisci equalize themselves on contact.

neal tear film that are described above in the in vitro experiments.

The lacrimal meniscus is best studied for these phenomena by placing fluorescein in the eyes and observing the region of the lower eyelid with the cobalt blue filter under high power. One notes the concavity of the meniscus and that the surface layer is rather rigid. Immediately above the meniscus on the cornea is the line of thinning manifested by a dark line of less fluorescein (Fig. 7). When the lower eyelid is pushed up, the meniscus and the thinned area above it also move up. A similar thinning is noted in association with the meniscus of the upper eyelid. When the two eyelids are made to come together, the two thinned areas merge (Fig. 8).

Menisci with their adjacent thinning are also noted surrounding bubbles in the tear film (Fig. 9), and also surrounding pieces of mucus (Fig. 10) or pus, which elevate the surface and may be trapped in the film. Contact lenses are surrounded by a meniscus with an area of thinning (Fig. 11). As these objects are moved, the meniscus and the induced thinned region move also.

It is a regular observation that when tear-film fracture occurs in an eye under observation, it occurs in an area of meniscus-induced thinning, similar to that occurring in vitro. When the film fractures in the thinned area, the film rapidly retracts from the initial fracture site along the line of thinning. As has been previously described,[1,4] the dried area resists wetting and causes a hich contact angle to form before the resistance is finally overcome by pushing up the lower eyelid. When the fluorescein-stained meniscus finally wets such a dried cornea, it leaves a delicate linear superficial stain corresponding to the dried line. Such areas of superficial staining were seen to develop naturally

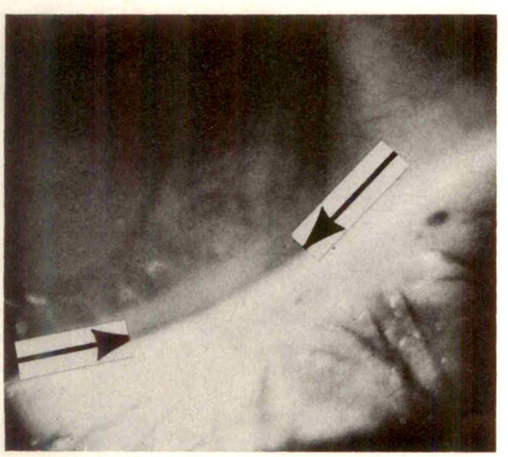


Fig. 7 (McDonald and Brubaker). Line of meniscus-induced thinning (arrow) is seen just above the meniscus in this fluorescein-stained tear film.

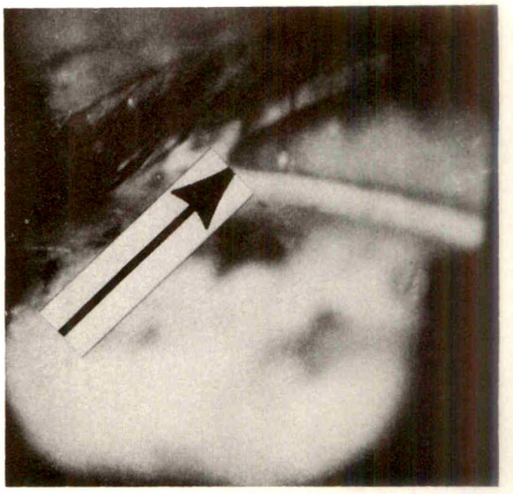


Fig. 8 (McDonald and Brubaker). Meniscus-induced thinning of the upper and lower eyelid seem to reinforce each other to produce extensive thinning.

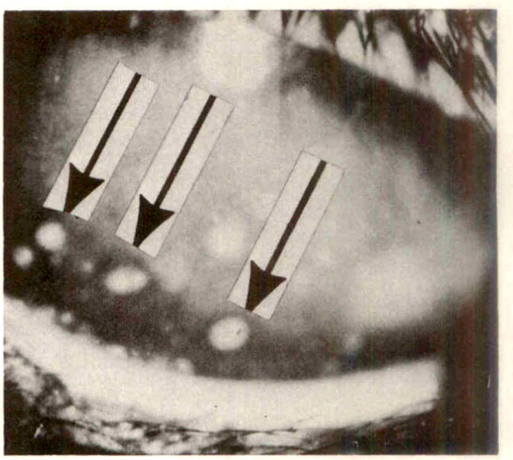


Fig. 9 (McDonald and Brubaker). Bubbles in a rabbit tear film show minisci which are surrounded by rings of thinning (arrow).

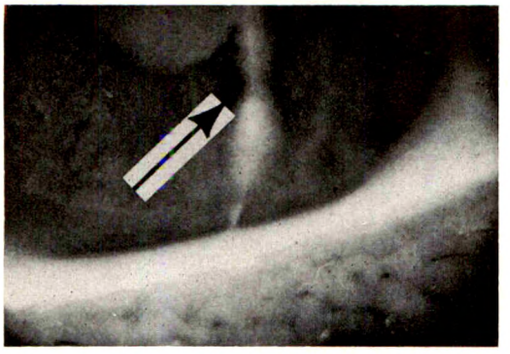


Fig. 10 (McDonald and Brubaker). Mucus on the cornea raises a meniscus which is surrounded by an area of thinning (arrow) in the fluorescein-stained film.

just above the lower eyelid meniscus without any necessity of the eyelid being pushed up.

The circular thinned film surrounding the meniscus of a contact lens acts similarly. It is in this thinned film that fracture of the film usually occurs in a contact lens wearer. The superficial staining frequently seen from three to five o'clock and from seven to nine o'clock in contact lens wearers was seen to develop by film fracture in the thinned film adjacent to the meniscus.

In a fluorescein-stained tear film observed with the blue light of the slit lamp, the thin area acts like a subsurface vacuum cleaner. If the lower eyelid is raised, the fluorescein-stained aqueous phase of the tear film shoots rapidly through the thinned area into the meniscus, just as the fat particles were seen to speed through this area into the meniscus in vitro. The surface oil layer remains immobile. From the direction of movement one can conclude that the hydrostatic pressure is lower in the thinned region than in the tear film, and that it is even lower in the meniscus. This sucking phenomenon of the thinned film is even more striking in conjunctivitis, when cellular debris dramatizes the rapid flow.

If the lower eyelid is then lowered, the tear film remains thinned over a wide area until it thickens by interlaminar flow from the thicker parts of the film, or is made even again by a rapid blink of the upper eyelid. The effect of gravity is negligible, as evidenced by the fact that the same phenomenon can be seen on the upper eyelid meniscus.

When the meniscus and its thinned film from the lower eyelid touch the meniscus of a contact lens, it frequently drains much of the volume of fluid from the contact lens both from its meniscus and the fluid under it.

## Discussion

The concept that negative pressure sucks fluid from stretched film faster than it can be replaced and thereby induces thinning of a film appears logical. It is compatible with present ideas on capillarity and foam and bubble drainage.[10] The more acutely curved (the shorter the radius of curvature) a meniscus is, the greater is the reduction in pressure inside the fluid as compared to the gas or nearby fluid. The simple situation relating to the reduction of pressure in the meniscus of a capillary tube is shown in the following equation of capillarity:

$$\Delta P = \gamma \ (1/r_1 + 1/r_2)$$

In this equation, $\Delta P$ equals the reduction of pressure inside the fluid, $\gamma$ equals the surface tension, $r_1$ equals the radius of curvature of the meniscus, and $r_2$ equals the radius of curvature in the meniscus in a plane at right angles to the plane of $r_1$. In a capillary tube,

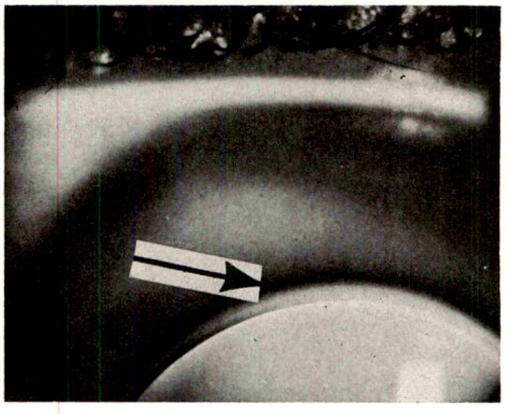


Fig. 11 (McDonald and Brubaker). Contact lenses are always surrounded by a meniscus, which in turn is surrounded by a ring of tear-film thinning (arrow).

if the meniscus is assumed to be hemispherical, $r_1$ and $r_2$ are equal, and the equation reduces to $\Delta P = 2\ \gamma/r$. Using this equation, Ehlers[1] calculated a $\Delta P$ of about 4.5 mm of water between the fluid in the precorneal film and the meniscus. He concluded that this pressure difference will "suck fluid from the film and bring about a speedier reduction in the thickness of this film." We believe that he wrongly concludes that this pressure will "hardly have any effect on the interlaminar flow."

When both radii of curvature are drawn from the same side of the film (as in a capillary tube), $r_1$ and $r_2$ are positive, and both curvatures contribute to the suction effect. In the case of the eyelids, the curvature of the tear film meniscus in the vertical axis ($r_1$) is not helped by any contribution of curvature in the horizontal plane. In this case, $r_2$ becomes very large and $1/r_2$ is almost nothing. In the case of the meniscus of a contact lens, $r_1$ contributes to the suction, but $r_2$ in the plane of the lens is drawn from the other side of the meniscus, and is therefore negative. This second curvature subtracts from the suction effect of the primary curve. Any meniscus so drawn around the periphery of an object should therefore have less suction than one of the same primary curvature located on a straight or concave line. For this reason an eyelid meniscus of a given curvature can drain a contact lens meniscus of the same curvature as well as the weaker menisci around the periphery of curved objects.

This mechanism seems a most likely explanation for the normal renewal of the aqueous phase of the tear film (Fig. 12). The low-pressure menisci of the upper and lower eyelids suck the subsurface fluid into themselves. The thinning is a manifestation of this sucking, because the tear film cannot replenish the aspirated fluid fast enough by interlaminar flow. As the eyelids move across the cornea, this wave of low pressure in the thinned areas and menisci of the eyelids acts like a subsurface vacuum cleaner, since the film is too thin to depend on gravitational forces for renewal. This mechanism

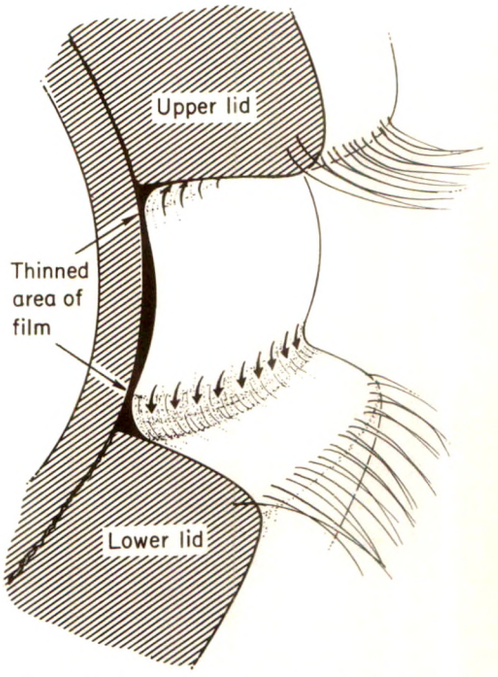



Fig. 12 (McDonald and Brubaker). Negative pressure in the meniscus thins the adjacent tear film. The blinking of the eyelids acts as a subsurface vacuum cleaner resulting in renewal of the aqueous phase of the tears.

is compatible with the fact that the surface oil layer does not participate in this fluid movement.

It is interesting that a "thirsty" meniscus (small radius of curvature) will take fluid from one with a larger radius of curvature in vitro and in vivo. This may act as a servomechanism. When the meniscus gets larger and less curved, it gets less "thirsty." When the eyelid's meniscus gets drained by the puncta and canaliculi, it becomes more curved and commences to "vacuum" under the surface more strongly.

In many patients, especially the elderly, one frequently sees a delicate linear horizontal staining just above the lower limbus. Observations on these eyes suggest that tear film fracture in the thin area of the lower eyelid meniscus may be the underlying cause of this condition.

The commonly observed staining in the inferior nasal and temporal quadrants near, but not under, contact lenses may be due to

tear film fracture induced by the additive effects of the thinning associated with the contact lens meniscus and the lower eyelid meniscus. Film fracture in these areas also may be partly due to the upper eyelid being kept away from the epithelium, resulting in poor wettability of the cornea, possibly due to a surface deficiency of phospholipids[1] or mucus.[7] This explanation seems more likely than the explanation that this staining is a manifestation of too loose or too tight a fit of the contact lenses.

It may be that burning and superficial staining of conjunctivitis may be due to tear film weakness, associated with the meniscus of mucus or debris in the tear film. Indeed, anything which causes a meniscus, such as a high pterygium, a successful filtering bleb, swollen limbal tissue after muscle surgery, might by this mechanism contribute to tear film fragility and staining and even dellen sometimes seen in these conditions.

## Summary

There is a thinning of fluid films adjacent to concave menisci both in vitro and in the tear film. Films fracture preferentially in these thin areas.

Menisci of the eyelids, of contact lens, of bubbles and mucus or debris in the tear film, or of adjacent perilimbal elevations such as filtering blebs, all have an adjacent area of thinning where film fracture and resultant staining often occur.

This sucking action of the eyelid menisci seems to be a basic mechanism for subsurface tear renewal.

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# LYMPHATIC DRAINAGE FROM VASCULARIZED RABBIT CORNEA

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Although it is generally acknowledged that the nonvascularized cornea does not have cell-lined lymphatic vessels, the presence of lymphatics in the vascularized cornea seems to be indicated by the experimental work of Collin,[1] Busacca,[2] Mann and associates,[3] Aoki,[4] and Katayama.[5] In corneal transplantation, vascularization of the host cornea is associated with a high incidence of graft rejection. To evaluate the role of the lymphatics in this unfortunate phenomenon, it is important to determine the nature of the lymphatic drainage in vascularized corneas. This preliminary objective may serve as a basis for future studies of the role of sensitized regional lymph nodes in the graft rejection phenomenon. This we have attempted to do in rabbit corneas by the intrallamellar injection of India ink.

## MATERIALS AND METHODS

The experimental animals were seven pigmented adult male rabbits, each weighing five pounds. Vascularization was induced in the corneas of rabbits 1-4 by gentle swabbing with a cotton-tipped applicator soaked in 20% sodium hydroxide solution. Corneal edema and vascularization developed rapidly, then quieted down and stabilized in from two to three weeks.

At this point we injected the right eye of rabbit No. 1 with bovine gamma globulin (BGG). The BGG was dissolved in physiologic saline solution and filtered through a millipore filter; the concentration of the final solution was 30 mg/ml. Intravitreal inoculation of approximately 0.05 ml (1.5 mg) of this solution (with a 27-gauge needle attached to a 0.25-ml tuberculin syringe) was followed by subconjunctival injection of 1 ml of India ink (previously boiled, diluted, and filtered) in the same eye. Five days later the animal was killed, and the preauricular and cervical lymph nodes were excised from the surrounding tissue.

Both eyes of rabbits 2-7 (three with vascularized corneas and three with nonvascularized corneas) then received similar intrav-



Fig. 1 (Smolin and Hyndiuk). Black discoloration of regional lymph nodes (preauricular and cervical).

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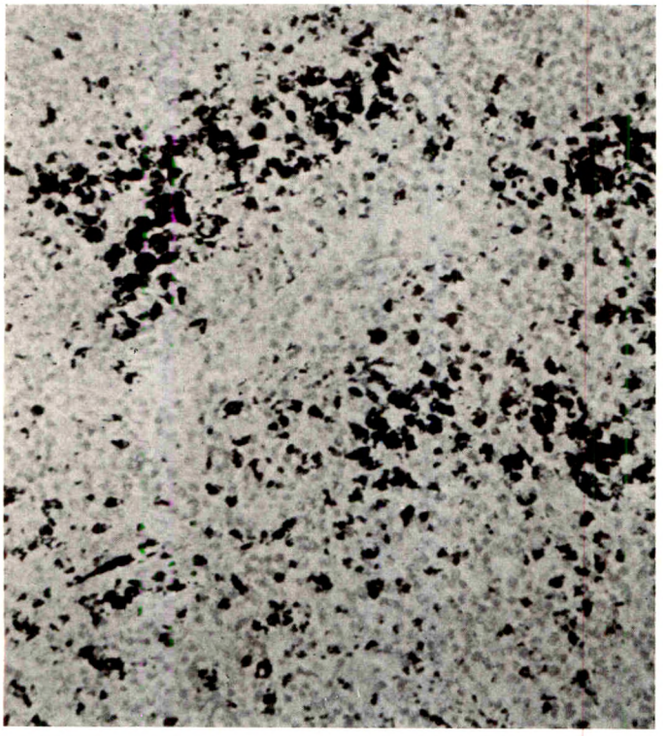


Fig. 2 (Smolin and Hyndiuk). India ink particles in regional lymph node (×200).

itreal inoculations of BGG. This was followed by intralamellar injections of India ink in the right eyes only, as follows: A fixation forceps was used to grasp the limbal conjunctiva at the 11 o'clock position, and 0.05 ml of India ink was injected through a 30-gauge needle into the corneal mid-stroma. The animals were killed five days later. The "draining" lymph nodes and corneas were first photographed in situ and then excised for histologic study.

## Results

The preauricular and cervical lymph nodes of rabbits 1-7 were enlarged. This was attributed to the animals' reaction to the BGG inoculation. Gross examination of the nodes of rabbit No. 1 revealed a black coloration (Fig. 1), and histologic examination revealed an abundance of India ink particles (Fig. 2).

In the nonvascularized corneas of rabbits 5-7, the depot of India ink remained at the site of inoculation (Fig. 3). The isolated lymph nodes were enlarged, but no black coloration would be seen either grossly or on histologic examination of stained or unstained sections (Fig. 4). Histologic examination of the nonvascularized corneas was also negative: There were no cell-lined channels filled with India ink (Fig. 5).

In the vascularized corneas of rabbits 2-4, there was immediate dispersion of the India ink in a linear, branch-like configuration. This pattern was still in evidence on day five

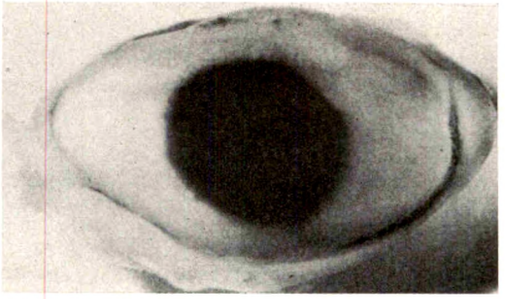


Fig. 3 (Smolin and Hyndiuk). Rabbit cornea with depot of India ink (×2).

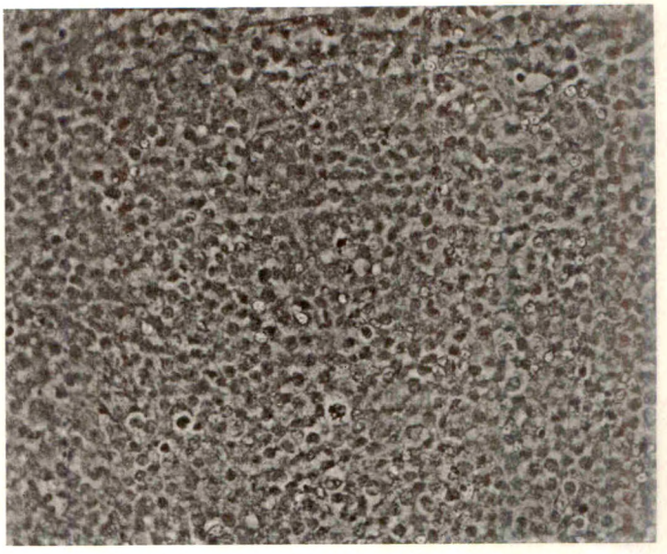


Fig. 4 (Smolin and Hyndiuk). Negative-phase photomicrograph. Regional lymph node showing no evidence of India ink (×400).

when the animals were killed (Fig. 6). When the enlarged lymph nodes were excised and examined grossly, none of them looked discolored. When unstained sections were examined histologically, India ink was absent from the lymph nodes on the left side, but present in small quantities in those on the right side (Fig. 7). Histologic examination of the vascularized corneas revealed channels infrequently filled with India ink and devoid of red blood cells (Fig. 8)

## Discussion

Preauricular and cervical lymph nodes were usually difficult to identify in the rabbit. The intravitreal inoculation of BGG enlarged the nodes and thus facilitated their identification and removal. BGG was injected intravitreally into the left eye of rabbits 2-7 as a control, in order to show that it had no influence on the lymphatic drainage from the cornea. India ink was selected because of the satisfactory way in which it out-

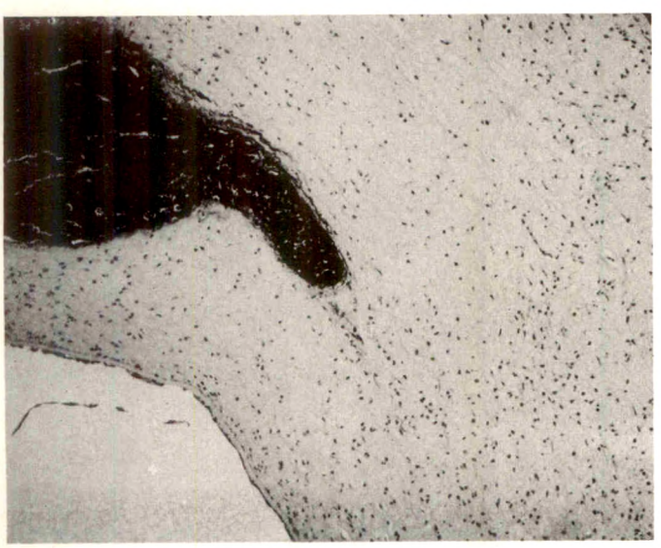


Fig. 5 (Smolin and Hyndiuk). Rabbit cornea with depot of India ink (×100).

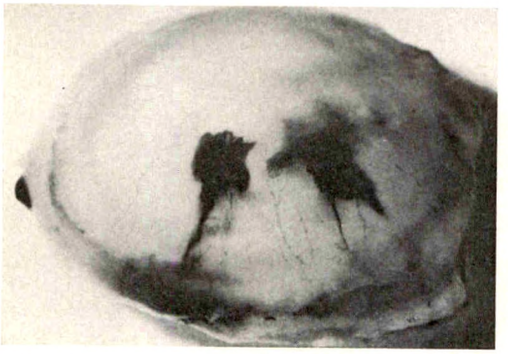


Fig. 6 (Smolin and Hyndiuk). Spread of India ink in rabbit cornea (×2).

lines lymphatic vessels.[4] Mandarin Ink,[1] Patient Blue V,[1] Evans blue,[6] and other dyes have also been used effectively for this purpose in the past.

The passage of India ink to lymph nodes on the right side and not on the left indicates that spread of the dye was localized. These results are consistent with those obtained by Collin[6] in his experiments with rats.

In the nonvascularized corneas India ink was not present in detectable amounts at the limbus or in the lymph nodes. This was consistent with the belief that although cell-lined lymphatic vessels are not present in nonvascularized corneas, they may be present in vascularized corneas and may play a significant role in the passages of large-sized particles from the cornea, as for example, India ink.

In Polack's[7] opinion, corneal antigens can diffuse through the cornea toward the limbal vasculature, and neither blood vessels nor lymphatic vessels in the cornea are necessary for sensitization of the host. We believe that this concept is at least partially correct. Corneal antigens may diffuse toward the limbus in the manner suggested, but we feel that corneal lymphatics, when present, play the major role in the transfer. The obvious application of this concept is in keratoplasty. We know that marked vascularization of the recipient cornea is a serious threat to the survival of the grafted cornea. If lymphatic vessels were transporting soluble corneal antigens to the regional lymph nodes as they can transport India ink, then local treatment of the graft might alter the afferent arc of the sensitization process associated with transplantation, and rejection might be prevented. According to Lambert's[8] experimental evidence, the lymphatic system is important in the spread of tissue antigens, and others[9-12] have shown that continuous local treatment of the graft site may alter the rejection phenomenon. However, periodic local treatment seems to have no effect.[13]

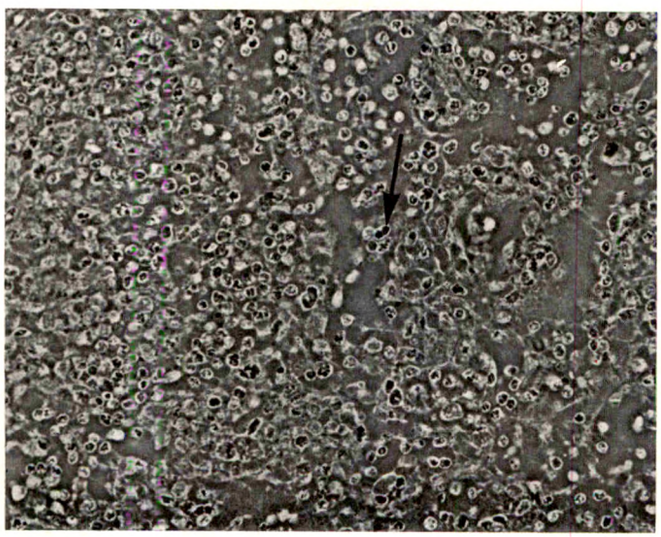


Fig. 7 (Smolin and Hyndiuk). Negative-phase photomicrograph. Regional lymph node with small amount of India ink (×400).

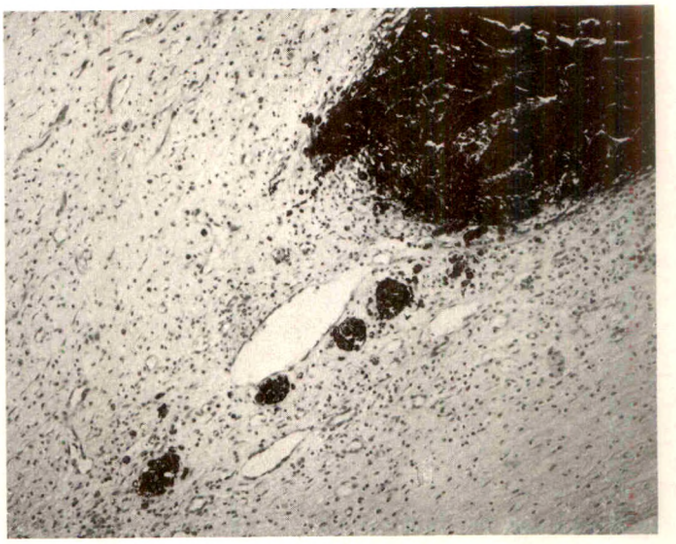


Fig. 8 (Smolin and Hyndiuk). Rabbit cornea with channels filled with India ink (×100).


## Summary

Intralamellar injection of India ink into vascularized rabbit corneas was followed by rapid spread of the material to the limbus and ipsilateral regional lymph nodes. In nonvascularized corneas no such spread occurred.


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# SPECTACLE GLASS INJURIES TO THE EYE

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The common place familiarity of spectacles tends to lessen our concern for them as a source of lacerations or burns.[1] The immediate demands of the surgical repair of an injured eye tend to preempt our attention away from the cause of the injury. Unfortunately, neither coding systems nor the vast majority of patient records identify causative mechanisms or the source of glass when trauma or foreign-body injury is noted on hospital charts. Further, it may be difficult, either on the basis of history or examination, to differentiate spectacle glass fragments from windshield, bottle, window, or other glass sources. Thus, on the basis of literature review, Duke-Elder[2] contended that the incidence of ocular injury from spectacles was relatively rare. This, however, is contradicted by personal experience and surveys of trauma initiated by the National Society for the Prevention of Blindness.[3,4]

In the enormous literature on ocular trauma, causative details are often ignored. At other times, when glass is named as the cause of injury,[5] the source of the glass is not identified. Frequently, cases of spectacle glass foreign bodies[6] are found only on critical reading of reports such as those by Laibson[7] (one in five, Thorpe[8] (one in five), Roper-Hall[9] (in a primarily industrial study, one in 555), McDonald and Ashodian[10] (one goggle in four), Sornson and Brown[11] (six in 270), Kaufman[12] (nine "regular spectacle glass" in 1107 industrial injuries), or Burke[13] (two cases in discussion). In 1958, Dickinson[14] reported 36 cases of spectacle glass injury. Occasional reports deal with unique aspects of an individual spectacle glass injury,[15,16] or detection of spectacle glass foreign bodies.[17]

This report of 42 injured patients (Table 1) covers personal and institutional experience from May, 1964, through November, 1970. This is an underestimation of total experience because the mechanism of injury or the type of glass are impossible to determine in some cases. Several additional cases have been brought to our attention by others who knew of our interest in this subject.

In this series, there were 37 males and five females, or a male/female ratio of seven to one. Ages ranged from eight to 72 years, with the highest incidence in the second decade of life, and fairly even distribution throughout all other of the first five decades. Causes of these spectacle glass injuries varied widely (Table 2), but only six injuries could be considered occupational. Refractive errors extend upward to +6.00 D, but the majority are in the moderately myopic range of −1.00 to −3.00 D. A total of 57 surgical procedures have thus far been performed on these injured eyes and a few more may yet be necessary. Despite extensive ophthalmic care, 12 eyes are now legally blind and three more may meet this fate in time—or a total of one-third of this series.

Three of these patients were treated entirely as outpatients; three more had unusually long military hospitalizations of 90, 90, and 150 days. In the remaining 36 cases, average length of hospitalization was nearly 11 days—or approximately 390 days of hospital and medical care expense that need not have been incurred.

In each of these patients, it appears that ocular damage could have been prevented by heat-tempered, impact-resistant, glass lenses, or even more certainly by allyl resin lenses.[18,19] Laboratory study a decade ago[20] suggested that high-density or heavy, small

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TABLE 1

SPECTACLE GLASS INJURIES

| Patient | Age | Mechanism of Injury | Principal Damage | Operations | Treatment | Current Vision | Days in Hospital |
|---|---|---|---|---|---|---|---|
| 1 | 49 | Auto crash | Limbal and scleral perforations; glass in corneal stroma, sclera and AC; cataract | 3 | Repair of wounds, glaucoma surgery, removal of glass from sclera, cataract removal | 20/50 | 29 |
| 2 | 39 | Fist | Perforating corneal laceration, iris prolapse, traumatic cataract | 2 | Repair of cornea and iris prolapse, iridocapsulotomy | 20/30 | 9 |
| 3 | 25 | Nail | Corneal perforation, glass in AC, traumatic cataract | 1 | Repair of cornea, removal of glass, aspiration of lens | 20/200 | 11 |
| 4 | 12 | BB pellet | Perforating corneal laceration, iris prolapse, glass in AC, traumatic cataract | 2 | Repair of cornea and iris prolapse, removal of glass from AC twice | Hand movements | 16 |
| 5 | 18 | Fall | Conjunctival and scleral lacerations | 1 | Repair of sclera and conjunctiva | 20/30 | 3 |
| 6 | 10 | Rock | Perforating corneal laceration, glass in AC | 1 | Repair of cornea, removal of glass from AC | 20/20 | 6 |
| 7 | 11 | Rock | Multiple superficial corneal lacerations, multiple embedded glass, traumatic hyphema | 1 | Removal of glass from cornea, medical control of hyphema | 20/70 | 7 |
| 8 | 43 | ? | Multiple lacerations of eyelids, traumatic hyphema | 1 | Repair of both eyelids, medical control of hyphema | 20/30 | 4 |
| 9 | 39 | Fist | Conjunctival and scleral lacerations, glass embedded in sclera | 1 | Removal of glass, repair of sclera and conjunctiva | 20/40 | 4 |
| 10 | 14 | Walked into tree branch | Perforating corneal laceration, iris prolapse, glass in AC, traumatic hyphema, and cataract | 2 | Repair of cornea and iris prolapse, removal of glass, medical treatment | Light perception | 33 |
| 11 | 68 | Wood from electric saw (occupational) | Corneal laceration, bacterial endophthalmitis | 1 | Repair of cornea, medical treatment | 20/70 | 10 |
| 12 | 35 | Fist | Lacerations of eyelids, conjunctiva and sclera; intraocular glass; vitreous hemorrhage | 1 | Repair of lacerations, removal of glass | Light perception | 6 |

TABLE 1 (*Cont'd*)

| Patient | Age | Mechanism of Injury | Principal Damage | Operations | Treatment | Current Vision | Days in Hospital |
|---|---|---|---|---|---|---|---|
| 13 | 10 | BB pellet | Perforating corneal laceration, iris prolapse, intraocular glass, retinal detachment and massive vitreous retraction | 1 | Repair of cornea and iris prolapse, removal of glass | Hand movements | 9 |
| 14 | 49 | Flying debris | Lacerations of eyelids, corneal laceration, embedded glass in cornea | 1 | Removal of glass, repair of eyelid lacerations | 20/70 | 24 |
| 15 | 72 | Wood | Perforating corneal laceration, glass in AC, traumatic cataract | 1 | Removal of glass, medical care | 20/80 | 6 |
| 16 | 35 | Assault | Superficial corneal lacerations, glass in conjunctiva | 1 | Removal of glass | 20/100 (amblyopia) | 4 |
| 17 | 27 | Baseball | Superficial eyelid and corneal lacerations, glass embedded in cornea | 1 | Removal of glass, medical care | 20/25 | Outpatient only |
| 18 | 28 | Pliers (occupational) | Perforating corneal laceration, glass in AC, fragments in corneal stroma | 1 | Removal of glass, repair of cornea | 20/30– | 6 |
| 19 | 22 | ? | Perforating corneal wound, glass in AC | 3 | Removal of glass | 20/50– | 150* |
| 20 | 16 | Fist | Perforating corneal wound, glass in AC | | Medical care | 20/30– | 4 |
| 21 | 54 | Assault | Perforating corneal and scleral lacerations, iridodialysis and iris prolapse, hyphema, eyelid lacerations | 2 | Repair of cornea and sclera, excision of iris prolapse, repair of eyelid | | 9 |
| 22 | 27 | Jack handle (occupational) | Multiple, superficial corneal lacerations; embedded glass | 1 | Removal of glass, medical care | 20/15 (corrected†) 20/25 (corrected§) | 90* |
| 23 | 19 | Plastic bomb | Multiple embedded glass fragments, superficial and deep corneal scars (bilateral) | 3 | Removal of glass, medical care | 20/30 20/20 | 90* |

* U.S. Army.
† Contact lens.
§ Spectacles.

TABLE 1 (*Cont'd*)

| Patient | Age | Mechanism of Injury | Principal Damage | Operations | Treatment | Current Vision | Days in Hospital |
|---|---|---|---|---|---|---|---|
| 24 | 43 | Bow | Perforating corneal and scleral lacerations, iris prolapse, vitreous hemorrhage, cataract, enophthalmitis, embedded glass, choroidal rupture | 2 | Excision of iris prolapse, removal of glass, wound repair, cataract extraction, medical care | 20/40 | 13 |
| 25 | 13 | Fall on ice | Perforating corneal wounds; glass embedded in stroma, angle and iris; post-subcapsular cataract | 1 | Removal of glass, medical care | 20/200 | 7 |
| 26 | 54 | Golf ball | Perforating corneal laceration, intraocular glass, traumatic cataract, adherent leukoma | 2 | Repair of cornea, removal of glass, removal of cataract | 2/200 | 6 |
| 27 | 8 | Rock | Superficial corneal lacerations, embedded glass in conjunctiva and cornea | 1 | Removal of fragments, medical care | 20/25 | Outpatient only |
| 28 | 28 | Falling tool (occupational) | Superficial eyelid, Conjunctival and corneal lacerations, glass in cornea | 1 | Removal of glass fragments | | 2 |
| 29 | 10 | Rock | Perforating corneal lacerations, traumatic cataract, glass in AC, lens and cornea, angle recession | 2 | Removal of glass, repair of cornea, sector iridectomy, removal of glass | 2/200 | 9 (?) |
| 30 | 25 | Masonry nail (occupational) | Perforating corneal laceration, traumatic cataract, glass in lens | 1 | Removal of glass, repair of cornea, spontaneous lens absorption | 20/20 with aphakic contact lens | 10 |
| 31 | 48 | Fist | Perforating corneal laceration, traumatic cataract, secondary glaucoma | 3 | Repair of cornea, 2nd stage repair, cataract extraction | | 15<br>7<br>12 |
| 32 | 11 | Volley ball | Superficial corneal lacerations, glass embedded in cornea | 1 | Removal of glass, medical care | 20/30 | Outpatient only |
| 33 | 15 | BB pellet | Perforating wound of limbus, iridodialysis, vitreous hemorrhage, glass in vitreous | 1 | Repair of limbal wound | 5/200 | 3 |

TABLE 1 (*Cont'd*)

| Patient | Age | Mechanism of Injury | Principal Damage | Operations | Treatment | Current Vision | Days in Hospital |
|---|---|---|---|---|---|---|---|
| 34 | 21 | Rock struck sunglasses | Corneal laceration, iris incarceration, eyebrow abrasions | 0 | Medical care, mydriatics, antibiotics | 20/40 | 6 |
| 35 | 57 | Brass fragment thrown from lathe (occupational) | Perforating corneal wound, eyelid laceration, iris prolapse, multiple foreign bodies, traumatic cataract, anterior synechia | 2 | Excision of prolapse, repair of cornea, cataract extraction | Hand motion | 25 |
| 36 | 31 | Assault | Perforated cornea, localized traumatic cataract, eyelid lacerations | 1 | Suture and repair of multiple corneal wounds | 20/30 | 6 |
| 37 | 22 | Attack | Corneal laceration, scleral laceration, deep skin cuts over malar eminence | 2 | Removal of glass, suture of sclera under general anesthesia | 6/9 | 7 |
| 38 | 14 | BB pellet | Perforating corneal laceration, dense cataract, multiple glass fragments in vitreous, vitreous hemorrhage | 1 | Repair of corneal laceration (glass not removed from vitreous) | LP | 6 |
| 39 | 48 | Golf club | Perforating corneal laceration, glass in AC and corneal stroma | 1 | Removal of glass, suture of corneal laceration | 20/60 | 7 |
| 40 | 40 | Steering wheel | Left upper eyelid, scleral and corneal laceration, cataract, endophthalmitis | 1 | Repair of cornea and eyelid, excision of iris prolapse | LP | 38 |
| 41 | 25 | Broom handle | Laceration of eyelid and cornea, glass in stroma | 1 | Removal of glass, suture of eyelid | 20/20– | 7 |
| 42 | 46 | Champagne cork | Laceration of cornea, iris prolapse, traumatic cataract, glass in AC | 1 | Removal of glass, reduction of prolapse, aspiration of cataract, suture of wound | 20/20 (corrected) | 4 |

foreign bodies (1 to 2 mm in diameter) traveling at high velocities (1200 to 1800 feet per second) might more easily penetrate tempered than nontempered glass. Such lens behavior under these unique circumstances seemed possibly related to slightly increased brittleness of heat-tempered glass in comparison to greater elasticity in nontempered glass. All such studies have shown greater impact resistance (per mm of thickness) in allyl resin lenses than in heat-tempered or conventional crown glass for both small, high-velocity missiles and larger, low-velocity missiles.[21] Decades of substantial industrial experience,

however, have documented the great value of heat-tempered glass in saving thousands of eyes.

Less frequently, spectacle glass injuries result when the lens is dislodged but unbroken. Eyelid or adnexal lacerations may be produced by posterior dislocation of an intact (safety or non-safety) lens from the eyepiece of a spectacle frame not affording a posterior retaining lip. In one patient in this series, a boy of 13 years, a baseball dislodged the right spectacle lens, which, in turn, caused a one-inch laceration beneath center of the right brow. The lens was not broken ($+2.00 - 4.50 \times 5 = 20/20$). The boy developed an infected hematoma with tenderness and swelling and a temperature of 104°F. After incision and evacuation under ketamine, healing, with the assistance of antibiotics, was uneventful. No bulbar damage was incurred.

Good safety frame design now includes a posterior lip on the eyepieces extending about 0.1 mm more centrally than does the anterior lip.[1] This requires that the lens be inserted from the front of the frame and makes it essentially impossible for a blow to dislocate the lens into the eye or adnexa.

Every frame should be made of nonflammable or fire-retardant materials, as are all industrial frames in this nation. Several foreign countries, however, still export frames made of highly flammable cellulose nitrate, which was outlawed both by the motion picture film industry and the Optical Manufacturers Association of this country many years ago.

Occasionally, opinion has been expressed that conventional crown spectacles offer more protection to the eye than no glasses at all. This may be true in the limited case of liquid splash accidents, but certainly, these 42 cases clearly indicate that the added protection of impact resistance should be an appropriate part of every spectacle prescription.

Fragile conventional crown glass and inadequately supporting frames should no longer be placed in hazardous proximity to the eye. Every pair of spectacles should be a protective armor to the irreplaceable human eye.

TABLE 2

CAUSE OF INJURY IN 42 CASES OF SPECTACLE GLASS INJURIES

| Cause | No. Patients |
|---|---|
| Assault (fist blows, 6) | 9 |
| Thrown rocks | 5 |
| BB pellets | 4 |
| Sports (volley ball, baseball, golf ball, golf club) | 4 |
| Falls | 2 |
| Nails | 2 |
| Wood, flying | 2 |
| Tree branch | 1 |
| Auto crash | 2 |
| Miscellaneous (broom handle, champagne cork, bow, pliers, plastic bomb, jack handle) | 6 |
| Occupational (all low velocity) | 6 |
| Unknown | 2 |

## SUMMARY

Forty-two patients are reported who sustained significant to blinding ocular injuries from spectacle glass fragments. Fifty-seven procedures have been required in treatment of these 42 patients, and a few additional operations may be anticipated. Only six of the total cases could be considered industrial. Males predominate by a ratio of 7 to 1. Both physicians' records and hospital charts generally fail to show causative details in ocular injuries. Also it is frequently impossible to differentiate glass fragments as deriving from spectacles versus windshields or bottles. Most of these injuries were preventable by the use of impact-resistant lenses and appropriately supporting posterior lip frames.

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# EYE INJURIES IN NIGERIA

## A Review of 433 Cases

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The incidence of blindness resulting from trauma has a worldwide variation. In some countries accidental trauma is the commonest cause of bilateral blindness,[1-3] while in other countries trauma rarely causes blindness in both eyes.[4-7] There are no comparable figures for Nigeria. The University College Hospital, Ibadan, serves a cross section of the Nigerian population. Nigeria is predominantly an agricultural country. The aim of this paper is to report on the causes of traumatic blindness in this community and to show how local situations affect ocular morbidity from trauma.

### Material and Method

In the period between 1963 and June 1970, there were 470 patients with traumatic blindness seen in the University College Hospital, Ibadan. Included in this number are 26 of 1000 consecutive patients blind in both eyes and 444 patients out of 2000 with uniocular blindness. Each patient was seen by an ophthalmologist and half of them were personally examined at subsequent visits. Thirty-seven patients were excluded from the series for inadequate information. All patients had sustained injuries resulting in reduction of visual acuity to counting fingers at three feet or less at first visit. Eye injuries have been classified by a number of authors[8-10] but for this paper, a simplified classification has been used.

The interval between injury and consultation varied considerably but only 20% of the patients were seen within one week of eye injury. This long interval between injury and consultation was due to difficulty in getting expert medical attention in time or failure of the patient to make use of available facilities. Difficulty in financing long journeys was also a problem. Of the 433 patients, 294 had received no previous treatment until they reached University College Hospital; 122 had received first aid at a local dispensary, their nearest general hospital, or at a general medical practitioner's clinic; 17 had received initial surgical treatment elsewhere. A large number had applied traditional remedies and came to the hospital only after several days of unsuccessful treatment at home, or when intractable pain forced them to do so.

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### Age and sex distribution

There were 360 male patients (83.75%) and 73 (16.25%) female, a ratio of 5:1 (Fig. 1). This male preponderance is shown in studies from other countries.[1,11] In this study, however, the preponderance of males was only partly due to the greater number of male patients attending the eye clinic. Some activities that are causes of traumatic blindness are quite often limited to the male. The 30-month civil war during this period further increased the number of injured males; traumatic blindness was due to military activity in 79 men in this study. Ages ranged from five to 70 years. The largest number of injuries (146) occurred in the 20-30 year age group (33%); most of these patients were men and more than half (79) were soldiers. The next largest number of patients (110) were in the 10-20 year age group (Fig. 3). The incidence of eye injury fell rapidly after 40 years of age, with only a handful of patients in the 60-70 year age group. Detailed analysis of the age and sex distribution is shown in Figures 1 and 2.

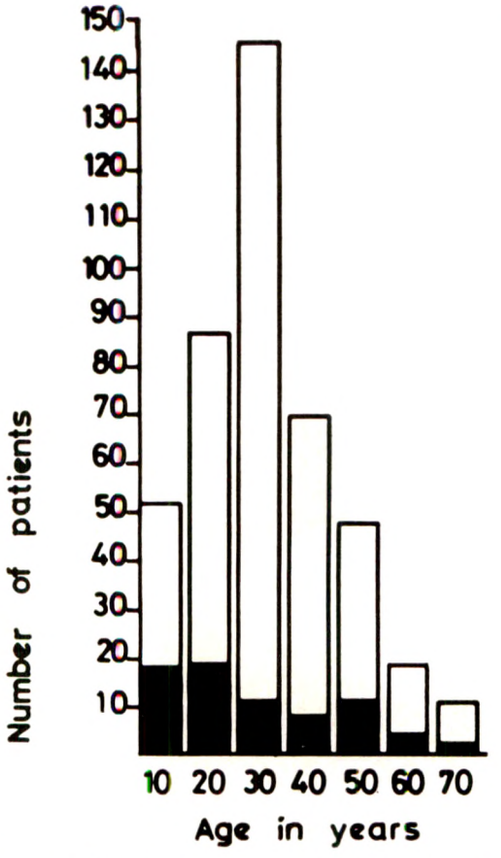



Fig. 1 (Olurin). Age and sex distribution in 433 patients. Key: white = males, black = females.

## Occupation

Patients were divided into 10 different occupational groups: (1) The category of "school children" included all young persons under the age of 20 years except those apprenticed at trades; (2) farmers; (3) industrial workers, including trade apprentices; (4) clerical office personnel; (5) executives and senior professionals; (6) housewives; (7) tradesmen; (8) soldiers; (9) old age pensioners; and (10) unemployed adults. The incidence of injury in each occupational group is shown in Table 1. The highest incidence was among soldiers (27.5%). Injuries in school-age children accounted for 25.4% of the total, and a more detailed study of the causes of injury in children is examined below. Farmers accounted for 24.5% of those injured. The country is still largely agricultural, and farming methods are not mechanized. The older methods of manual digging, hoeing and felling of trees make the farmer susceptable to some of the more serious types of eye injuries. A similarly high incidence of eye injury amongst farm workers was found in agricultural Ceylon,[12] where farming conditions are probably similar.

Industrial accidents accounted for 52 patients (12%), most of whom were employed in small-scale industries which abound in the country. Twenty-nine (6.7%) housewives sustained severe eye injuries mostly in the home. Activities that are probably peculiar to our way of life were responsible in 17 of these women: Nine were blinded by chips of palm kernels which they cracked manually in order to extract the seeds; eight were blinded while splitting firewood, often the job of the housewife in this country.

## Types and complications of injuries

Injuries were classified as perforations, contusions, or "others." Complications arising from each type of injury were as follows.

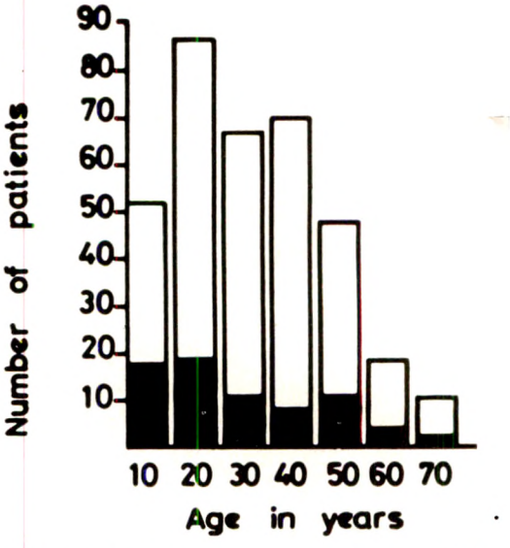



Fig. 2 (Olurin). Age and sex distribution in 354 patients (soldiers excluded). Key: white = males, black = females.

*Perforating injuries*—Perforation of the globe occurred in 242 patients (56%). On the whole, complications from these injuries were more severe than those following contusion injuries. Many perforating injuries were caused by gunshots and bomb blasts in soldiers, and these eyes were often shattered beyond repair, with surgery consisting principally of debridement and repair of the socket. Severe perforating injuries were also caused by wood (wood-splitting and twigs) during work on the farm. Such injuries were often complicated by large iris prolapses through lacerated cornea, traumatic cataracts, or sometimes loss of vitreous and the lens or both. Many farm injuries were complicated by severe endophthalmitis even when the injury itself did not seem severe.

*Contusion injuries*—These occurred in 162 patients (37.4%). The commonest complication was intraocular hemorrhage, which occurred in 65 patients. Vision was often lost from secondary intractable glaucoma, organization of blood in the anterior chamber, or blood staining of the cornea. Traumatic cataracts occurred in 60 patients with contusion injuries; subluxation of cataractous lenses occurred in 12 patients.

*Other injuries*—Endophthalmitis occurred in 27 patients. Ten of these cases were due to nonperforating injuries with hypopyon, which, with neglect, often proceeded to panophthalmitis. In 9 patients soil got in their eyes while digging or hoeing, and in these, infected corneal ulcers caused maceration and necrosis of the cornea. Four patients were blinded by burns, three by chemicals and one by fire. A detailed list of injuries and complications is shown in Table 2.

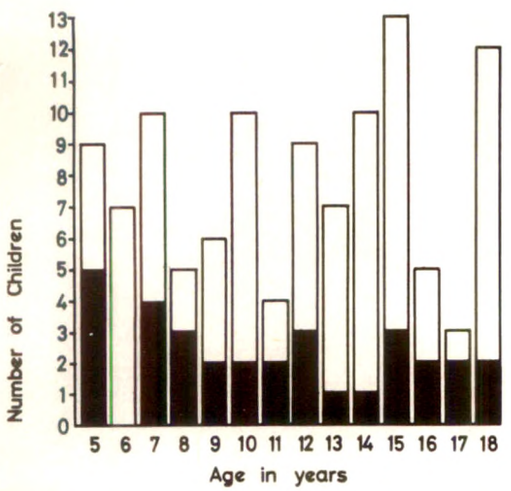



Fig. 3 (Olurin). Age and sex distribution in 110 children blinded by trauma. Key: white = males, black = females.

TABLE 1

INCIDENCE OF EYE INJURY BY OCCUPATIONAL GROUPS IN 433 PATIENTS

| Occupation | No. Patients | Percentage |
|---|---|---|
| School children | 110 | 25.4 |
| Farmers | 106 | 24.5 |
| Industrial workers | 52 | 12.0 |
| Medium grade office workers | 13 | 3.0 |
| Executives and professionals | 18 | 4.1 |
| Housewives | 29 | 6.7 |
| Tradesmen | 18 | 4.1 |
| Soldiers | 80 | 27.5 |
| Old age pensioners | 1 | 0.2 |
| Unemployed | 6 | 1.4 |
| Total | 433 | 100.0 |

*Occupational injuries*—These activities accounted for 212 injuries (49%), including those occurring during military service (Table 3). The total number of injuries sustained during occupational activities other than military service was 133 (30.6%). Household activities caused eye injuries in 98 (22.5%) patients. Play or sport accounted for injuries in 80 (18.5%) patients.

By far, the commonest agents were twigs, sticks, and pieces of wood, causing 182 (41.9%) severe eye injuries. Guns and explosives came next, causing 82 eye injuries —79 of these were in soldiers.

*Disability*—The rate of permanent disability was high. In this part of the country, people do not often come to the hospital for minor eye injuries, thus most of the injuries seen in the eye clinic are severe. There was no light perception in the injured eyes of 187

TABLE 2

TYPES OF EYE INJURIES AND COMPLICATIONS IN 433 PATIENTS

| Complications | Total No. | Percentage | Diagnosis | | |
|---|---|---|---|---|---|
| | | | Contusion Injuries | Penetrating Injuries | Others (Burns, Ulcers, etc.) |
| Intraocular hemorrhage | 65 | 15.0 | 65 | — | — |
| Traumatic cataracts | 94 | 21.7 | 60 | 34 | — |
| Secondary glaucoma | 45 | 10.25 | 37 | 8 | — |
| Ruptured globe | 8 | 1.7 | 8 | — | — |
| Luxation or subluxation of the lens | 12 | 2.8 | 12 | — | — |
| Retinal detachment | 3 | 0.7 | 3 | — | — |
| Endophthalmitis | 27 | 6.3 | — | 17 | 10 |
| Corneal necrosis, anterior staphyloma | 12 | 2.8 | — | 4 | 8 |
| Iris prolapse | 150 | 35.0 | — | 142 | 8 |
| Traumatic uveitis | 6 | 1.4 | 6 | — | — |
| Sympathetic ophthalmia | 2 | 0.46 | — | 2 | — |

patients when they were first seen. Many traumatic cataracts were associated with almost total occlusion of the pupil from secondary uveitis. In patients who had traumatic cataracts extracted, unilateral aphakia rendered the patient uniocular for most activities. Restoration of useful vision was therefore seen only in about 8% of the patients. Enucleation was the obvious treatment of choice in about 40% of the patients, but half of these refused the operation, preferring discomfort in a totally blind and a potentially

TABLE 3

ACTIVITY WHEN INJURED AND AGENTS CAUSING EYE INJURY IN 433 CASES

| | Male | Female | Total | Percentage |
|---|---|---|---|---|
| Activity: | | | | |
| Occupational | 122 | 11 | 133 | 30.0 |
| Military | 79 | — | 79 | 18.5 |
| Household | 60 | 38 | 98 | 22.5 |
| Play or Sport | 66 | 14 | 80 | 18.5 |
| Traffic or transport | 17 | 2 | 19 | 4.4 |
| Acts of violence and falls | 10 | 5 | 15 | 3.5 |
| Accidents in schoolroom | 6 | 3 | 9 | 2.0 |
| Total | 360 | 73 | 433 | 100.0 |
| Causes of accidents: | | | | |
| Twigs, sticks, pieces of wood, tree branches, grass blades | 159 | 40 | 199 | 44.9 |
| Cutlass or knife | 6 | 4 | 10 | 2.4 |
| Guns and explosives | 80 | 2 | 82 | 18.9 |
| Motor traffic accidents | 17 | 2 | 19 | 4.3 |
| Palm kernel chips | 6 | 9 | 15 | 3.5 |
| Injury by fingernail, hand, fist | 10 | 5 | 15 | 3.5 |
| Gravel | 8 | 1 | 9 | 2.1 |
| Tools and working materials | 21 | 2 | 23 | 5.4 |
| Other | 53 | 8 | 61 | 14.0 |
| Total | 360 | 73 | 433 | 100.0 |

dangerous eye. Twenty-six patients (20 males) were rendered blind in both eyes as a result of their injury (Table 4), but 10 of these were already blind in one eye from some earlier cause. Two patients lost second eyes from sympathetic ophthalmia. Seven patients were blinded by occupational injuries, seven were soldiers engaged in military activity, and six were blinded as a result of activities at home. Three of the totally blinded patients were children.

*Injury in school children*—There were 110 children studied in this group (Table 5). There were 78 boys and 32 girls, or a ratio of 2.4:1 (Fig. 3).

A large variety of agents caused eye injuries in these children, but these agents were different from those of other countries. In England, for example, Lambah[13] found that arrows, catapulted missiles, fireworks, and air gun pellets were responsible for the majority of eye injuries in the group he studied. They were rare causes of eye injury in our group. This is due to the difference in types of play and toys used in the two groups. Possibly, the pattern here will change with increased industrialization. There was no striking difference in the incidence of blindness in the different age groups. Injuries at play had the greatest incidence, accounting for 70 of 110 children. This included play at school and outside, but not inside, the home. There were 29 injuries in the home, three due to traffic accidents, and eight sustained in the classroom. Five classroom injuries were inflicted by a teacher's cane, one by a pen nib, one by a needle that penetrated the cornea, and one was caused by a blow delivered with a writing slate. Most boys were injured at play, whereas injuries in the home were relatively more common in girls. Perforating injuries were the commonest types of injury in children, occurring in 59 patients. Contusion injuries occurred in 41 children: falls, five; motor traffic accidents, three; chemical burns, one; and gravel, one. The types of complication and high rate of disability was similar to that seen in the adult group. Three children lost the sight of both eyes, one of them from sympathetic ophthalmia. This last child was the first patient in this clinic to have such a complication. The history was that of a neglected corneoscleral rupture by a door handle, with prolapse of uveal tissue, two months before consultation. There was a lower half corneociliary staphyloma and active uveitis in the uninjured eye on the first visit. Despite treatment with corticosteroids, the boy, aged 12, rapidly became blind. The only other occurrence of sympathetic ophthalmia in the series was in a 22-year-old soldier who refused enucleation after a retained intraocular foreign body in a blind, painful eye. Sympathetic ophthalmia is said to have a higher incidence amongst young persons.[14]

## Comments

Eye injuries are of major socioeconomic importance, particularly from the preventive view. The activity of the individual plays an important part in the cause of injury, hence causes of eye injuries in children differ from those in adults. The largest number of eye injuries in children are sustained at play; in this study they accounted for 70 of 110 (63.6%) cases. Many could have been prevented—such injuries include those from firearms, knives, cutlasses, and many of the injuries in the classroom and the home. Leisure activities, which featured prominently as causes of eye injury in adults in other studies,[1,11] were infrequent in this study, accounting for only 10 of 323 (3%) eye injuries. This perhaps reflects the mode of life in this community, where few adults engage in active sports, games, or active hobbies. Occupational activities (excluding military activities) accounted for 30% of ocular injuries in the study as a whole, and 40% of eye injuries in adults alone. Most of these were agricultural injuries. It is tempting to assume that with better agricultural methods such injuries would not occur, but even in Sweden with modern farming methods, Lindstedt[15] remarked on the high incidence

TABLE 4

BLINDNESS IN BOTH EYES DUE TO EYE INJURY
(26 patients)

| No. | Age | Sex | Occupation | Type of Activity | Cause of Injury | Type of Injury | Complication | Eyes Lost From Injury | Cause of Loss of First Eye |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 19 | Male | Mechanic | Traffic accident | Glass | Penetrating | Iris prolapse, corneal scarring, phthisis | Two | — |
| 2 | 45 | Male | Farmer | Occupational | Twig and plant juice | Corneal maceration | Anterior staphyloma | Two | — |
| 3 | 66 | Male | Farmer | Occupational | Twig | Penetrating | Traumatic cataract, endophthalmitis | One | Couching of cataract |
| 4 | 47 | Female | Trader | Wood splitting (home) | Piece of wood | Penetrating | Panophthalmitis | One | Keratitis |
| 5 | 27 | Male | Farmer | Occupational | Twig | Penetrating | Traumatic cataract and iridocyclites | One | Optic atrophy |
| 6 | 25 | Male | Stone mason | Violence | Chemical burns | Corneal ulceration | Corneal scarring | Two | — |
| 7 | 65 | Male | Farmer | Occupational | Tree branch | Contusion cataracts | Subluxated cataracts | Two | — |
| 8 | 35 | Male | Farmer | Occupational | Twig | Penetrating | Endophthalmitis | One | Chronic uveitis |
| 9 | 28 | Male | Soldier | Military | Gunshots | Penetrating | Phthisis | Two | — |
| 10 | 24 | Male | Soldier | Military | Bullet | Penetrating, nerve injury in fellow eye | Phthisis, one eye, optic atrophy, one eye | Two | — |
| 11 | 25 | Male | Soldier | Military | Bomb blast | Penetrating | Collapsed globes | Two | — |
| 12 | 12 | Male | Schoolboy | Home | Door handle | Ruptured globe | Sympathetic ophthalmia | Two | — |
| 13 | 7 | Male | Schoolboy | Home | Stick | Penetrating | Collapsed globe | One | Optic atrophy |
| 14 | 26 | Male | Soldier | Military | Bomb blast | Penetrating | Ruptured globes and collapse | Two | — |
| 15 | 30 | Female | Trader | Home | Fire burns | Corneal ulcers | Corneal scarring | Two | — |
| 16 | 30 | Female | Housewife | Violence | Chemical burns | Corneal ulcers | Corneal scarring | Two | — |
| 17 | 22 | Male | Soldier | Military | Bomb blast | Penetrating | Ruptured globes and collapse | Two | — |
| 18 | 35 | Male | Carpenter | Occupational | Blow with piece of wood | Contusion | Dislocated cataracts | One | Kerato conjunctivitis |
| 19 | 22 | Male | Soldier | Military | Gunshot | Penetrating | Sympathetic ophthalmia | Two | — |
| 20 | 21 | Male | Soldier | Military | Bullet | 1. Penetrating, one eye<br>2. Optic nerve injury, one eye | 1. Ruptured globe<br>2. Optic atrophy | Two | — |
| 21 | 32 | Male | Tax collector | Home | Piece of wood | Penetrating | Endophthalmitis | One | Old keratitis |
| 22 | 7 | Female | School child | Play | Stick | Penetrating | Endophthalmitis | One | Optic atrophy |
| 23 | 65 | Female | Housewife | Home | Fall | Contusion | Dislocated cataracts | One | Keratitis |
| 24 | 45 | Female | Housewife | Home | Piece of wood | Penetrating | Corneal scarring | One | Trachoma |
| 25 | 45 | Male | Industrial | Traffic accident | Chemical burns | Corneal ulcer | Corneal scarring | Two | — |
| 26 | 23 | Male | Carpenter | Occupational | Wood rot | Corneal ulcer | Perforation of corneas | Two | — |

of eye injury in branches of forestry and farming. Household activities caused eye injuries in 60 of 433 patients (22.5%); this was almost equally as common in males as females, and many could have been prevented.

The high rate of disability is due to a number of factors. The study is limited to the severer forms of eye injuries, because the majority of minor injuries are seen elsewhere. Often, the damage to the eye at time of injury was so severe that useful vision could not have been achieved whatever the treatment. Nevertheless, the long delay in seeking help was a contributing factor, especially in patients who developed secondary infection, or secondary glaucoma from hemorrhage and the like. All perforating injuries were severe and many involved tears and prolapse of uveal tissue, with incarceration for long periods. Some eyes remained inflammed for many weeks or even months. The low incidence of sympathetic ophthalmia is notable (2 out of 433 patients). In two other studies,[6,11] sympathetic ophthalmia was responsible for blindness in 2.8% and even 6.7%, although both authors stated that it rarely occurred after 1950. It is difficult to say whether or not the low incidence in the present study is due to racial immunity,[14] or whether the high rate of infection protected the patients in this series against sympathetic ophthalmia.

TABLE 5

CAUSES OF EYE INJURY IN 110 CHILDREN

| | Total No. | Percentage |
|---|---|---|
| Activity when injured: | | |
| Play activity | 70 (57 boys) | 63.6 |
| Home | 29 (13 boys) | 26.4 |
| Schoolroom | 8 (6 boys) | 7.3 |
| Traffic | 3 (2 boys) | 2.7 |
| Agent of injury: | | |
| Twigs, sticks, pieces of wood | 46 | |
| Cutlass and knife | 10 | |
| Fist | 7 | |
| Ball | 6 | |
| Whip | 5 | |
| Falls | 5 | |
| Motor vehicle | 3 | |
| Palm kernel chips | 3 | |
| Gunshot | 3 | |
| Catapults | 2 | |
| Rubber strips | 2 | |
| Nails | 2 | |
| Stones | 2 | |
| Needles | 2 | |
| Piece of bone | | |
| Tree branch | 1 | |
| Chemical burn | 1 | |
| Writing tablet | 1 | |
| Door handle | 1 | |
| Gravel | 1 | |
| Pen nib | 1 | |
| Rope | 1 | |
| Umbrella | 1 | |
| Thumbnail | 1 | |
| Cardboard | 1 | |
| Thorn | 1 | |

Although there have been no previous detailed reports on the causes and types of eye injuries in Nigeria, it is likely that the picture will be similar in all parts of this country except for the larger and newly industrialized towns. Eye injury in children will probably continue to be due to similar etiologic factors, but as the country gradually becomes more industrialized, it will be helpful to compare this study with future ones.

## SUMMARY

This report from the eye clinic of the University College Hospital, Ibadan, Nigeria, reviews 433 cases of severe eye injury seen between 1963 and 1970. It yields data in regard to the character, incidence, and causes of severe eye injury, and compares the results with studies from other countries. Eye injury in 110 children, accounting for a quarter of the series, has been studied separately and compared with injury in adults.

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OPHTHALMIC MINIATURE

Great men have a curious way of appearing in complementary pairs. This has happened so often in history that I don't think it can have been invented by symmetrically minded historians, but must represent some need to keep human faculties in balance. However that may be, there is no doubt that the two great musicians of the early eighteenth century, Bach and Handel, fall into this pattern of contrasting and complementary personalities. They were born in the same year—1685; they both went blind from copying musical scores and were operated on, unsuccessfully, by the same surgeon. But otherwise they were opposites.

Kenneth Clark
Civilisation

# ATYPICAL MYCOBACTERIA AND UVEITIS

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As part of a long-term study of the causes of uveitis, the responses of the sera of uveitis patients to the antigens from 12 strains of atypical mycobacteria were studied. Atypical mycobacteria, once thought harmless, are now known to produce granulomatous lesions.

Sera from uveitis patients are found to react with mycobacterial antigens more frequently than sera from any other group studied except patients with sarcoidosis.[1] The purpose of this paper is to attempt an explanation for this reactivity.

## MATERIALS AND METHOD

Undiluted sera from 364 patients with all types of uveitis and from 191 blood donors were subjected to agar diffusion against antigens from 12 strains of atypical mycobacterial.[1] The sera from the blood donors were supplied by the Indiana University Medical Center Blood Bank. The donors were unselected, and the only information given was age, sex, and that they met the usual criteria required for blood donation. The reactivity of a serum was measured by the number of precipitation lines formed in the agar between the serum and the antigen.

The atypical mycobacteria have been divided into four groups: the photochromogens, the scotochromogens, the nonchromogens, and the rapid growers. We were concerned only with the first three groups. The numbers following the P's in Table 1 refer to strains obtained from Runyon. PC, SC, and NC are mixtures. T6D6 is a wild strain isolated from muddy soil. The uveitis patients also received the battery of skin tests previously reported.[2]

TABLE 1

SEROLOGIC REACTIVITY TO GROUPS OF ATYPICAL MYCOBACTERIA BY UVEITIS PATIENTS AND BLOOD DONORS

| Antigens | Percent of Patients Reacting | |
|---|---|---|
| | Uveitis Patients (364) | Blood Donors (191) |
| Photochromogens (Group 1) PC, P1, P8 | 9.61 | 21.99 |
| Scotochromogens (Group 2) SC, P6, P15, T6D6 | 48.35 | 14.14 |
| Nonchromogens (Group 3) NC, P44, P2, P17, P39 | 53.02 | 19.90 |

## RESULTS

Table 1 shows that uveitis patients differ ($p < 0.001$) from blood donors in their reactivity to the three Runyon groups of atypical myobacteria. Since atypical mycobacteria are widespread and tend to have antigens in common, they were considered in groups. A reaction to one or more members of a group was considered a reaction to the group. Some patients and donors showed reactions to more than one group and are included in the figures for each group to which they showed reactivity.

The significance of a single precipitation

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TABLE 2

SEROLOGIC REACTIVITY TO ATYPICAL MYCOBACTERIA IN VARIOUS UVEITIS DIAGNOSTIC CATEGORIES

| Diagnostic Category | Percent of Patients Reacting | | | Total Cases |
|---|---|---|---|---|
| | Group 1* | Group 2* | Group 3* | |
| Histoplasmosis | 8.91 | 50.49 | 58.42 | 101 |
| Toxoplasmosis | 14.06 | 46.88 | 51.56 | 64 |
| Peripheral uveitis | 11.54 | 26.92 | 30.77 | 26 |
| Unknown etiology | 5.00 | 55.00 | 52.00 | 100 |
| All others | 12.33 | 45.20 | 56.16 | 73 |

* Group 1: PC, P1, P8 (photochromogens); Group 2: SC, P6, P15, T6D6 (scotochromogens); Group 3: NC, P44, P2, P17, P39 (nonchromogens).

line in the case of the mycobacteria is a matter of controversy. Some workers[1] believe that such a line is due to a nonspecific lipopolysaccaride. Others[3,4] feel that any line of precipitation must be accounted for. Since antigens from atypical mycobacteria are not pure, since the strains overlap, and since only two groups of patients (those with sarcoidosis and uveitis) show a preponderance of two or more lines of reactivity, we chose to define a reactor as an individual who showed two or more lines of reactivity as opposed to one or less lines of reactivity.

TABLE 3

FACTORS ANALYZED

1. Characteristics of the patients:
   - Age
   - Sex
   - Race
   - Place of residence (urban or rural)
2. Characteristics of the uveitis:
   - Type of inflammation (granulomatous or nongranulomatous)
   - Course of the disease (acute, chronic, or recurrent)
   - Severity of the disease (mild, moderate, or severe)
   - Site of the inflammation (anterior, posterior, or both)
   - Type of lesion (iritis, cyclitis, iridocyclitis, retinitis, choroiditis, chorioretinitis, papillitis, pars planitis, focal, disseminated or diffuse lesions)
   - Presence or absence of macular involvement
   - Presence or absence of prior trauma
3. Reactivity to any of 18 different skin tests
   - Sedimentation rate
   - Serum electrophoresis
   - Differential white blood cell count

The percentage of patients showing positive tests to atypical mycobacteria may be seen in Table 2. They are grouped by diagnostic category. Reactivity to more than one group was common. This was particularly true of Group 2 and Group 3.

No relationships could be found between reactivity to one or more atypical mycobacteria and any combination of factors (Table 3). In other words, we could not find a patient/disease pattern that could be linked with positive reactions to any of the positive mycobacteria.

We, therefore, investigated the possibility that the reactivity of uveitis patients to atypical mycobacteria might be due to the immunologic characteristics of the patients rather than to their disease process. Since we had already studied the immunologic characteristics of uveitis patients with respect to skin testing,[2] we decided to compare the skin test reactivity of these patients with their serum agar diffusion reactivity to atypical mycobacteria.

The measure of reactivity was a ratio. In the numerator was the number of tests positive, and in the denominator, the number of tests done. The number of skin tests done varied from 10 to 18. The number of agar diffusion tests was 10 or 12. We applied the Freeman-Tukey Angular Transformation to the ratios in order to obtain values suitable for statistical analysis.[2] This transformation is the method of choice for dealing with ratios, since it gives due weight to the denominators, which the use of percentages does

TABLE 4

AGE, DIAGNOSIS, AND PERCENTAGE REACTING TO SKIN AND AGAR DIFFUSION TESTS

| Age | | Histoplasmosis | | Toxoplasmosis | | Unknown Etiology | | Peripheral Uveitis | |
|---|---|---|---|---|---|---|---|---|---|
| 0–19 | Skin | 28.3% | 5 | 22.8% | 17 | 24.4% | 8 | 20.5% | 11 |
| | Agar | 24.5% | | 13.0% | | 18.3% | | 14.4% | |
| 20–29 | Skin | 36.9% | 25 | 28.6% | 16 | 31.0% | 13 | 34.1% | 7 |
| | Agar | 13.2% | | 14.0% | | 10.8% | | 7.3% | |
| 30–39 | Skin | 38.4% | 34 | 31.9% | 11 | 31.2% | 28 | 19.4% | 4 |
| | Agar | 16.1% | | 9.6% | | 14.3% | | 3.6% | |
| 40–49 | Skin | 41.5% | 23 | 42.7% | 13 | 26.4% | 21 | 25.3% | 7 |
| | Agar | 11.7% | | 12.2% | | 14.2% | | 4.9% | |
| 50–59 | Skin | 40.0% | 10 | 25.7% | 2 | 26.3% | 19 | 29.0% | 4 |
| | Agar | 12.4% | | 13.3% | | 10.5% | | 16.6% | |
| 60-up | Skin | 31.3% | 2 | 17.6% | 5 | 28.4% | 8 | 23.6% | 1 |
| | Agar | 27.0% | | 17.6% | | 14.5% | | 2.0% | |
| Total Cases | Skin* | 36.1% | 99 | 28.2% | 64 | 28.0% | 97 | 25.3% | 26 |
| | Agar* | 17.5% | | 13.3% | | 13.7% | | 8.9% | |

* Unweighted means.

not. For easier comparisons, however, values have been transformed into percentages in Table 4. Each cell contains the mean percent of positive reactors. It includes the positive reactors for the skin tests and the agar diffusion tests against atypical mycobacteria. Only those diagnostic categories were included which gave reasonable cell frequencies. This limited our study to the major types of uveitis seen. Age is included as a dimension since it has been found that skin test reactivity does vary with age.[2] The values were subjected to an analysis of variance. In regard to skin test reactivity both diagnosis and age were significantly different (Table 5) which confirms our previous report.[2]

The analysis for the agar diffusion results revealed that the diagnostic categories differed significantly, but there was no significant change with age of the patients (Table 6). The reason for this may be that whereas the

TABLE 5

SKIN TEST REACTIVITY/DIAGNOSTIC CATEGORY/AGE OF PATIENT ANALYSIS OF VARIANCE TABLE

| Source | df | Mean Square | F Ratio | Probability |
|---|---|---|---|---|
| Diagnosis | 3 | 43,460.0 | 5.574 | =0.0001 |
| Age | 5 | 44,487.8 | 5.706 | <0.001 |
| Error | 277 | 7,796.9 | | |

TABLE 6

AGAR REACTIVITY/DIAGNOSTIC CATEGORY/AGE OF PATIENT ANALYSIS OF VARIANCE TABLE

| Source | df | Mean Square | F Ratio | Probability |
|---|---|---|---|---|
| Diagnosis | 3 | 44,908.0 | 4.056 | <0.01 |
| Age | 5 | 10,774.8 | 0.970 | ns |
| Error | 277 | 11,070.5 | | |

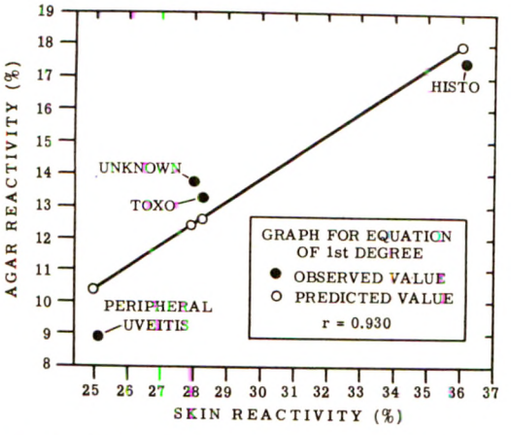



Fig. 1 (Weber, Schlaegel, and Chapman). Graph for equation of first degree.

reactivity to skin tests of all types falls off with age, the reaction to agar diffusion does not.

Linear regression analysis applied to the unweighted means (last row of Table 4) shows (Fig. 1) the relationship between the two measures of immunologic reactivity in the uveitis diagnostic groups. The positive correlation between the two measures ($r = 0.930$) is significant at the 5% level.

## Discussion

Patients with presumed histoplasmic choroiditis react to many antigens besides histoplasmosis—both by skin testing and by agar diffusion. Patients with peripheral uveitis react to very few antigens by either method. Those with toxoplasmosis and uveitis of unknown etiology are intermediate in reactivity on both measures (Fig. 1).

Another possible explanation for the presence of antibodies against atypical mycobacteria in patients with uveitis could be that these organisms may act somewhat in the nature of Freund's adjuvant with respect to some other antigen. Acid-fast organisms, either with or without an oil, may maintain some type of tissue contact which alters the initial reaction from one of simple inflammation to one of cellular hypersensitivity. Thus, in uveitis patients it is possible that atypical mycobacteria might potentiate other types of antigens.

## Summary

Undiluted sera from 364 uveitis patients of all types and 191 unselected blood donors were subjected to agar diffusion against antigens from 12 strains of atypical mycobacteria. The sera of uveitis patients were significantly more reactive to the scotochromogens and nonchromogens and less reactive to the photochromogens ($p < 0.001$) than were the sera of blood donors.

No patient-disease pattern could be linked with positive reactions to any of the atypical mycobacteria.

Comparison of the reactivity of the uveitis patients to a battery of 10 to 18 skin test antigens and the reactivity of their sera to the atypical mycobacteria showed: (1) Patients with presumed histoplasmic choroiditis are highly reactive to both types of antigens; (2) patients with peripheral uveitis react to very few antigens of either type; (3) patients with toxoplasmosis or uveitis of unknown etiology are intermediate in both types of reactivity.

The reactivity of uveitis patients to atypical mycobacteria appears to be a reflection of their immunologic characteristics rather than their disease process. This leads us to postulate that the atypical mycobacteria are rarely, if ever, a direct cause of clinical uveitis.

### Acknowledgments

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# DIAGNOSIS OF CRYPTOCOCCAL UVEITIS WITH HYPERTONIC MEDIA

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Eye symptoms have been reported ot occur in 44 per cent of patients with cryptococcal meningitis including blurred vision, retrobulbar pain, diplopia and photophobia.[1] Such symptoms are most often due to extraocular causes and reflect elevated cerebrospinal fluid pressure or extraocular muscle paresis. Less often symptoms are due to intraocular infection with Cryptococcus neoformans; occasionally the infection may extend directly along the subarachnoid space into the optic nerve, producing optic neuritis,[2] uveitis, and keratitis,[3] Involvement of the orbit from contiguous skin lesions is rare.[4–6]

The purposes of this report are to present an additional case of probable cryptococcal uveitis and to emphasize the value of the latex slide agglutination test for detecting cryptococcal antigen and the use of hypertonic sucrose media for cultural identification.

## CASE REPORT

A 58-year-old charter boat operator from Montauk, Long Island, developed spots in the visual field of his right eye and retro-orbital pain in February, 1967. He was subsequently noted to have right anterior and posterior uveitis and was managed over a five-month period with triamcinolone in doses varying from 8 to 32 mg daily. During therapy he developed progressive loss of right eye vision and physical findings of severe right chorioretinitis. He was admitted to South Hampton Hospital, Long Island, July 3, 1967, with fever and three days of vertigo with a tendency to fall to the right. While hospitalized it was discovered that a tuberculin test was positive and that the cerebrospinal fluid was abnormal (sugar, 26 mg%; total protein, 268 mg%; white count, 244 $mm^3$ with 114 PMNs and 130 lymphocytes; serology, negative).

July 18, 1967, he was admitted to St. Luke's Hospital Center because of continuing fever. Ophthalmic examination revealed a total retinal detachment in the right eye with severe inflammatory reaction in the vitreous and what appeared to be active inflammatory foci in the retina. There was a 3+ flare and cells in the anterior chamber; a small pupil in this eye was bound down by posterior synechiae. The corrected vision was 20/20 in the left eye and there was absent right light perception. Intraocular pressure was RE: 8 mm Hg, and LE: 14 mm Hg. The vertigo had resolved and the neurologic examination was within normal limits. The hemoglobin was 14.9 g% and the white blood count 18,000 $mm^3$ with a normal differential count. Urine analysis was normal. The serum alkaline phosphatase was 11 King-Armstrong units and a two-hour postprandial sugar was 135 mg%. Protein electrophoresis revealed a gamma globulin level of 790 mg%. A brain scan ($^{99}Tc$) and echoencephalogram were essentially normal. Chest x-ray examination revealed normal lung fields. On July 27, 1967, signs of an abdominal right lower quadrant infection appeared and laparotomy revealed a right lower quadrant appendiceal abscess which improved following surgical drainage and treatment with antibiotics. Retrospectively it appeared likely that the entire febrile course might have been related to the appendiceal abscess.

Six cerebrospinal fluid examinations during this admission were performed. Cultures for Mycobacterium tuberculosis and Cryptococcus neoformans were repeatedly negative. Attempted isolation of fungi included culture at 25° and 37°C on four media: Sabourand-glucose, blood, Littman oxgall and brain-heart infusion agar. Cryptococcal antigen and antibody studies were performed by Dr. Morris Gordon of the New York State Department of Health: The presence of 1:4 spinal fluid and 1:2 serum cryptococcal antigen titers suggested a cryptococcal infection. In view of a positive PPD reaction, intermediate strength, and the failure to isolate a fungus, the patient was discharged on August 31, 1967, on antituberculosis therapy.

The cerebrospinal fluid abnormalities remained essentially unchanged after three months. The spinal fluid of July 26 cultured in hypertonic sucrose media (M/0.3 sucrose in brain-heart infusion broth, enriched with 10% horse serum) to explore the possible presence of microbial L forms showed tiny colonies of two types when subcultured on blood agar,

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one appearing microscopically like cells of Candida and the other appearing diphtheroid-like. Both were considered contaminants and were placed in the refrigerator. Two months later the colonies were again examined. The small colonies containing Candida-like cells all now showed typical encapsulated cryptococci. The diphtheroid-like colonies were unchanged; 10 of these were transferred to blood agar on different days; each of these, on subculture, appeared as large mucoid colonies consisting of typical encapsulated cryptococci. Subsequently, this isolate was definitely identified as mouse-virulent C. neoformans. It appeared likely that the uveitis was due to an infection with this agent, although mycologic studies of the eye were not performed. Amphotericin B therapy was initiated on November 7 with increasing intravenous doses administered daily together with 25 mg of hydrocortisone in an infusion over three hours for a total dose of 2.0 gm. Spinal fluid cultures on February 9 and 24, and September 23, 1968, were negative on hypertonic sucrose media. His right eye became quiet and comfortable but remained without light perception. Visualization of the posterior segment was not possible due to cataract lens changes and vitreous opacification.

## Comments

Review of the literature reveals at least 13 previously reported cases of probable cryptococcal uveitis since 1948.[1,7-17]

Of the previously reported cases, in nine there was histologic evidence of cryptococcal involvement of the uveal tract. In three cases, the eyes were not examined histopathologically[1,13,15] and in the case reported by Weiss and associates[7] pathologic examination revealed only granulomatous inflammation.

Two additional unreported cases of cryptococcal uveitis are on file in the registry of Ophthalmic Pathology.[16] In addition, one of us (D.B.F.) has recently seen a 65-year-old Caucasian woman who presented with acute right hemiplegia followed in several weeks by anterior and posterior uveitis as well as retinal detachment. Subsequent autopsy revealed C. neoformans meningoencephalitis but the eye was not examined.

## Pathogenesis

The intraocular structures may be involved either by direct extension from the central nervous system along the meningeal sheaths of the optic nerve of via the blood stream from a localized or disseminated cryptococcal infection. An important observation is that in each of the seven cases in which culture results are reported, C. neoformans was cultured from the spinal fluid. This, cryptococcal uveitis is frequently accompanied by meningeal involvement indicating that eye involvement usually results from spread along the optic nerve. Whether the ocular involvement starts in the retina or choroid, or in some cases, as simultaneous involvement of both structures, is difficult to establish. Since C. neoformans has a marked affinity for the brain and meninges, perhaps the sensory retina may also be extraordinarily susceptible to cryptococcal invasion. Cryptococcosis often complicates malignant lymphoma, and three of 13 patients had a reticuloendothelial malignancy, an incidence of 23%. An additional patient was a premature infant and another was in her third trimester of pregnancy. Eleven of the 13 previous patients have been males. There was no evidence to suggest augmentation of infection by antibiotics, corticosteroids or antimetabolites.

## Diagnosis

The patient presented here, without underlying disease, developed cryptococcal uveitis associated with transient dizziness but without physical findings of focal neurologic involvement. A routine cerebrospinal fluid examination revealed increased lymphocytes and protein and decreased glucose and choloride but the etiologic agent escaped isolation by routine culture.

Examination of the cerebrospinal fluid reported in eight of these patients was consistently abnormal. This indicates that cerebrospinal fluid examination is essential to the diagnosis of cryptococcal uveitis and should be considered in the evaluation of any patient with persistent uveitis of undetermined etiology, especially if progressive deterioration occurs despite corticosteroid therapy. Of the 14 reported cases, this is the ninth to be diagnosed during life. The diagnosis was suggested in this patient by progressive uveitis

despite triamcinolone therapy, abnormal spinal fluid, and the presence of cryptococcal antigen in the serum and CSF and later verified by hypertonic sucrose media culture.

Delayed reactions to cryptococcin skin test antigen frequently occur in patients with active cryptococcosis, with treated, inactive cryptococcosis, or with exposure to cryptococci in the environment, but the test may be positive in apparently normal persons. Epidemologic data are thus far fragmentary, and the skin test cannot yet be utilized to suggest the diagnosis of active cryptococcal infection.[18-20] The determination of cerebrospinal fluid alcohol concentration is unlikely to be helpful since strains of C. neoformans vary markedly in alcohol production.[21]

A significant development was the description of a complement-fixation test to detect circulating cryptococcal polysaccharide.[22] More recently Gordon and Vedder[23] found that a latex slide agglutination test for cryptococcal antigen was sensitive and specific as a diagnostic tool. Studies for cryptococcal antigen are most effective when used in conjunction with whole yeast cell agglutination tests for cryptococcal antibody since there appears to be an inverse relationship between the two. Of 14 cases in which specimens of body fluid, usually both serum and CSF, were obtained during the period of positive cryptococcal cultures, antigen was demonstrated in 11, antibody in two, and neither in one. Both the latex slide agglutination test for cryptococcal antigen and the whole-cell agglutination test for cryptococcal antibodies appear to be highly specific. Similar results have been reported by Bindschadler and Bennett[24] in 75 patients with cryptococcosis using an indirect fluorescent test for serum anticryptococcal antibody and a complement fixation test for serum and cerebrospinal fluid cryptococcal antigen. Although the CF test for antigen has been specific for cryptococcosis, a few false-positive tests for antibody were found. The presence of cryptococcal antigen in the spinal fluid and serum of the patients reported here definitely helped to lead to the correct diagnosis. The spontaneous decrease in titer prior to the institution of amphotericin B therapy is worthy of note but remains unexplained.

It has been previously emphasized that cryptococci may be isolated with difficulty from some patients with cryptococcal meningitis and that it is important in these cases to plant a large volume of spinal fluid on each of several small flasks of agar. Use of a flask of agar permits a long incubation period without undue evaporation of water from the medium.[25] The recovery of an aberrant form of C. neoformans from cerebrospinal fluid has been reported once previously, but no details of the other patient has been reported.[26] The value of cultivating for wall deficient microbial variants by using hypertonic media which protect the organisms from osmotic stress has also been shown to be useful in another yeast infection. In three instances, wall defective forms of Candida have been recovered from human blood.[27-28] Watanakunakorn and associates[27] grew Candida parapsilosis from blood in hypertonic media at a time when routine cultures were negative. Rosner[28] recovered L forms from the blood of a patient with endocarditis; after multiple subcultures these organisms reverted to a strain of Candida tropicalis. An extensive discussion of clinical infections associated with the isolation of aberrant forms of bacteria and fungi including a presentation of the bacteriologic findings in this case was recently published.[29]

Since chemotherapy with amphotericin B is available for the therapy of infections due to C. neoformans, it is important to consider this etiology in the evaluation of patients with uveitis of undetermined etiology, particularly if the disease progresses despite corticosteroid therapy. The majority of cases will be detected by cerebrospinal fluid examination and examination of the fluid and serum for cryptococcal antigen. In the presence of abnormal cerebrospinal fluid findings and a negative culture, diagnosis may be established by culture on hypertonic sucrose media.

## Summary

A probable case of cryptococcal uveitis is reported. The frequent occurrence of meningeal involvement is indicated by abnormal cerebrospinal fluid findings and cultural isolation of Cryptococcus neoformans in all patients in which these studies have been presented. The value of cultivating for wall-deficient microbial variants by using hypertonic media had been previously demonstrated in candidiasis and is further supported by the recovery of aberrant forms of C. neoformans in the cerebrospinal fluid of this patient. The usefulness of the latex slide agglutination test for detecting cryptococcal antigen is again emphasized.

Since chemotherapy with amphotericin B is available for the therapy of infections due to this organism, it is important to consider it in the evaluation of patients with uveitis of undetermined etiology, especially when corticosteroid therapy is ineffective.


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# OCULAR TOXIN OF THE PNEUMOCOCCUS

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Although the pneumococcus often is cited as an example of an organism which produces disease purely by means of its invasiveness, there are in the literature numerous suggestions of toxic activity on the part of this organism. These include reports by Shumway and Polack[1] of spherocytic anemia in rabbits infected with pneumococci or treated with concentrates of hemolysin; a report by Halbert and associates[2] of lethal and dermonecrotic effects of the purified hemolysin upon injection into the mouse; a report by Dick and Gemmell[3] of a variety of toxic effects produced following intraperitoneal injection of pneumococci; and a report by Blackman and associates[4] of acute nephritis produced by means of a pneumococcal autolystate. The extensive damage to corneal tissue and the hypopyon which characterize pneumococcal infection of the cornea suggested to us that toxic factors might play a role also in the pathogenesis of pneumococcal ulcer. This paper reports an experimental investigation of this possibility.

## MATERIALS AND METHODS

*Preparation and treatment of extract*—The organism used was an encapsulated Type XXI strain of Diplococcus pneumoniae isolated from a corneal ulcer and maintained in the lyophilized state. Pathogenicity of this strain for the rabbit eye was demonstrated by production of keratitis following intracorneal injection of about $10^6$ viable organisms. In agreement with the results of many other investigators, we found that instillation of viable bacteria ($10^9$) onto the conjunctiva of the rabbit did not produce conjunctivitis.

The bacteria were cultivated in filtered trypticase soy broth with 1 g per liter of $CaCO_3$ and harvested by centrifugation in the late exponential or early stationary phase of growth. The cells were washed with phosphate-buffered saline and stored at −60° C. Cell-free extracts (containing 3-5 mg protein/ml) were prepared in the Mickle cell disintegrator or by use of the French pressure cell, followed by centrifugation to remove whole cells and debris. When necessary, sterilization of the extract was accomplished by Millipore filtration.

Concentration of extracellular proteins in the culture fluid was effected after removal of cells by addition of ammonium sulfate to 90% saturation, stirring for several hours or overnight, redissolving the precipitate, and dialyzing against distilled water or buffer.

Protein content of these preparations was determined by the method of Lowry.[5]

For extraction of lipoidal material, the crude cell-free extract was lyophilized (a procedure which does not destroy toxicity) and then extracted five times with chloroform-methanol (2:1, v/v). After evaporation of the solvent, the extracted material was emulsified in phosphate-buffered saline. Separation of polysaccharide components of the extract was effected by addition of two volumes of ethanol, followed by centrifugation. The water-soluble portion of the precipitated material was diluted with phosphate-buffered saline before testing. Pneumococcal capsular polysaccharide was isolated from trypticase soy culture medium by the method described by Kabat.[6]

In treatment of the extract with deoxyribonuclease, 1 ml was incubated for 30 minutes at 0° C. with 0.05 mg salmon sperm de-

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oxyribonuclease (Calbiochem, A grade). Treatment with trypsin was accomplished by incubation of 1 ml of extract at 37° C. for 60 minutes with 0.5 mg enzyme (Worthington, TRL 6JA).

*Animal experiments*—Tests for toxic activity of the extracts were made on the eyes of adult albino rabbits. Variability in the response of different animals to the same preparation made it necessary to use one eye of each rabbit as a control on the level of response of that individual. Conjunctival instillation was accomplished by dropping the sterile preparation into the eye at a rate of 1 drop (approximately 0.05 ml) every 20 minutes. Intracorneal injection was effected with a 30-gauge needle after instillation of local anesthetic (Ophthaine).

*Enzyme assays*—Enzyme assays were performed as follows: hyaluronidase and chondroitinase by the method of Nakada and associates.[7] Keratanase was assayed by incubating 1 ml of extract with 2 ml 0.05 M buffer (acetate, pH 4.0, citrate, pH 5.5, or Tris-HCl, pH 7.8) and 2 mg keratosulfate for periods up to 12 hours, followed by measurement of release of reducing sugar by the method of Nelson[8] and amino sugar by a modification of the Elson-Morgan reaction described by Ashwell and associates[9] for 2-acet-amido hexoses. Both β-galactosidase[10] and β-acetylglucosaminidase[11] were assayed by the methods described by Hughes and Jeanloz. Lipase was assayed by the method of Lawrence and associates.[12] Proteinase was assayed by incubation of 0.5 ml crude extract with 0.5 ml 0.2 M buffer (acetate, pH 5.3 or Tris-HCl 7.5 or pH 8.8) and 0.5 ml of 2% diazocasein for 60 minutes at 37° C, followed by the addition of 3.5 ml 5% trichloracetic acid, filtration, addition of 0.5 ml 0.5 M NaOH, and reading of optical density in the Klett colorimeter with the blue filter, or by incubation with 2% gelatin followed by detection of the release of amino acids by the ninhydrin reaction as described by Hirs.[13] Peptidase was measured by incubation of 0.1 ml extract with 0.5 ml of leucyl-glycyl-glycine (2.5 mg/ml) and 0.4 ml Tris-HCl buffer (pH 7.5, 0.1 M), followed by removal of samples at varying time intervals for determination of liberated amino acids by the ninhydrin reaction as described above. Phospholipase C was assayed by the method of Kushner,[14] employing egg yolk saline, purified lecithin, or sphingomyelin. Activity was measured also in the presence of 0.01 M $Ca^{++}$, $Mg^{++}$, or $Co^{++}$.

*Hemolysin assay*—Hemolytic activity was determined with rabbit erythrocytes washed twice with phosphate-buffered saline and suspended in the same medium at a concentration of about 2%. Varying levels of extract were incubated with 1.5 ml erythrocyte suspension plus phosphate-buffered saline to a total volume of 3 ml for 30 minutes at 37° C with frequent gentle shaking. The intact cells were then sedimented by centrifugation and the hemoglobin in the supernatant layer estimated by reading the optical density at 541 mμ on a Bausch and Lomb Spectronic 20 spectrophotimeter. The $HD_{50}$ (amount of extract producing 50% hemolysis) was read from a plot of extract concentration vs optical density in the region from 20 to 75% hemolysis where this relationship is linear.

## Results and discussion

Instillation of sterile crude extract into the rabbit eye produced swelling, redness of the conjunctiva, and a purulent discharge (Fig. 1). The purulent material showed a typical acute inflammatory pattern with polymorphonuclear leukocytes predominating. These symptoms appeared in from 45 minutes to two hours after the first drop was instilled, depending on the strength of the extract and varying also from one rabbit to another. The treated eye appeared normal on the next day except for the presence of considerable quantities of dried purulent material.

When 0.01 to 0.02 ml of sterile extract was injected intracorneally, the response elicited included the above signs plus diffuse

corneal haze, iritis, and circumcorneal injection (Fig. 2). These signs appeared shortly after the injection, were even more severe at 24 hours when an extensive corneal opacity was observed (Fig. 3), and persisted for several days, leaving a small amount of residual scarring at 13 days. The control inoculation of phosphate-buffered saline produced a transient corneal haze, considerably less extensive than that in the test eye, and which was almost entirely clear in a few hours.

The properties of the toxic factor or factors responsible for the production of these effects have been studied by subjecting the extract to a variety of physical and chemical procedures and observing their effect on toxic activity. The results of this study are shown in Table 1.

Exhaustive dialysis (24 hours with a 5000-fold ratio of dialysand to dialysate) against buffer or water did not reduce the toxic activity of the extract as measured by the effect produced upon conjunctival instillation, indicating that the toxicity is due to the presence of a relatively large molecule. The effects produced upon intracorneal inoculation also were not reduced by previous dialysis of the extract. The factor was relatively heatstable, being only partially inactivated after three minutes at 100° C and still showing some capacity to provoke production of purulent discharge after 10 minutes at 100 ° C. The results of testing toxic activity of a chloroform-methanol extract of the preparation indicated that the material is not lipoidal, and the results of the alcohol treatment indicated that it is not a polysaccharide. Also, conjunctival instillation of purified

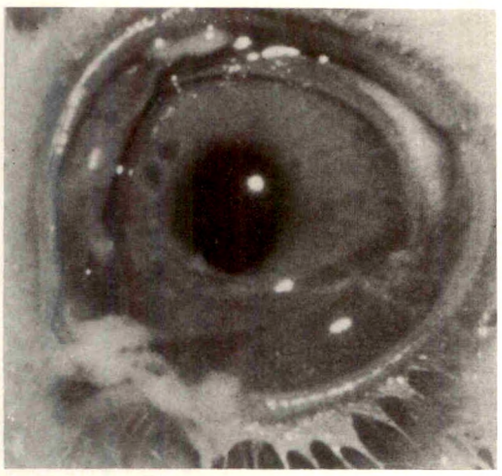


Fig. 1 (Johnson and Allen). Ocular inflammation resulting from conjunctival instillation of pneumococcal extract.

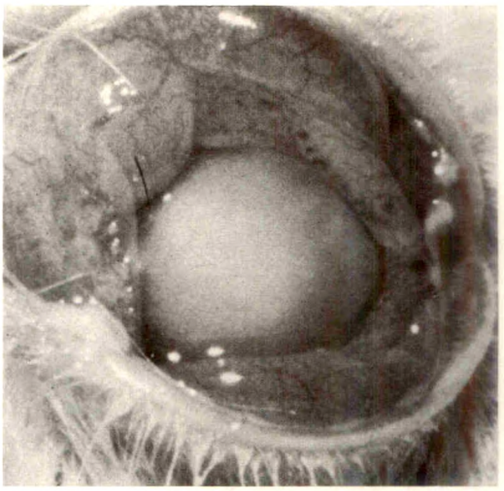


Fig. 2 (Johnson and Allen). Appearance of rabbit eye three hours after intracorneal injection of pneumococcal extract.

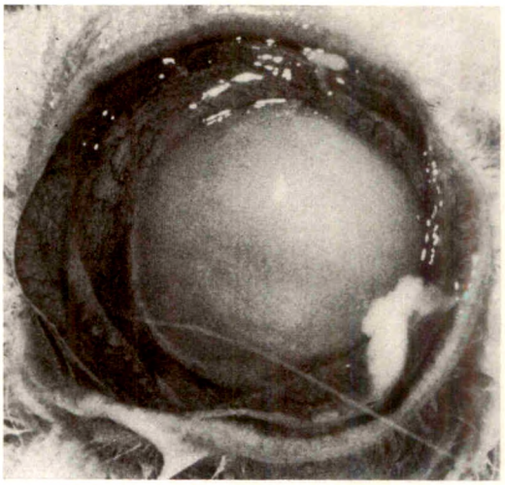


Fig. 3 (Johnson and Allen). Appearance of rabbit eye 24 hours after intracorneal injection of pneumococcal extract.

TABLE 1

EFFECTS OF VARIOUS PROCEDURES ON TOXIC ACTIVITY OF EXTRACT

| Procedure | Fraction Tested | Results (Activity upon conjunctival instillation as compared to untreated extract) |
|---|---|---|
| Dialysis* | Dialysate | Full |
| Dilution | | Delayed response |
| Heating | | |
| ( 3′ at 55°C) | | Full |
| ( 3′ at 100°C) | | Decrease in D, S, R† |
| (10′ at 100°C) | | Decrease D, little or no S, R |
| Chloroform-methanol extraction | Extractables (emulsified) | None |
| Alcohol precipitation | Alcohol insoluble, water soluble | None |
| Isolation of capsular polysaccharide | | None |
| Precipitation with 90% ammonium sulfate* | Precipitatable material | Full |
| Treatment with DNase | | Full |
| Treatment with trypsin | | None |

* Also tested by intracorneal injection.

† D, S, R: production of discharge, swelling, and redness, respectively, upon conjunctival instillation.

capsular polysaccharide produced no response. The precipitability by ammonium sulfate (confirmed also for intracorneal toxic activity) and the susceptibility to trypsin strongly suggest that the toxic material is protein in nature, although its heat stability is unusual for a protein.

A concentrate of ammonium-sulfate-precipitable constituents of the culture medium prepared after removal of cells did not produce a toxic effect. Therefore, we assume that the factor is normally part of the intact pneumococcal cell body. Different methods of cell treatment have been examined in order to study conditions under which the factor might be released from the cell. The results of these experiments are shown in Table 2. No detectable toxin was released from freshly harvested exponential phase cells as evidenced by lack of response to the instillation of unbroken cells. Toxin was relased when the cells were allowed to grow into stationary phase, or when the cells were stored, or when the cells were frozen as judged by the response to instillation of unbroken cells. We conclude that some release of toxin takes place under many types of suboptimal conditions.

In an attempt to determine the nature of the toxic factor, we have studied numerous degradative activities of the pneumococcal extract (Table 3). Hyaluronidase activity was present, as one would expect in a pneumococcus. The level of activity was not very high, however, and was not increased by inclusion of hyaluronate in the growth medium. No chondroitinase activity was detected by this method, even when cells were grown in the presence of chondroitin sulfate. Since most of the corneal mucopolysaccharide is keratan sulfate, exhaustive tests for keratanase activity were conducted. No activity was detected in cell extracts tested at pH 4, 5.5, or 8, even when keratan sulfate was included in the growth medium. Glycosidases which are capable of hydrolyzing

TABLE 2

EFFECT OF VARIOUS METHODS OF CELL TREATMENT ON TOXIC ACTIVITY

| Preparation of Cells | Toxic Activity (as compared to that of crude extract) |
|---|---|
| Freshly harvested, mid-exponential phase | Whole cells—none<br>Broken cells—full |
| Freshly harvested, early stationary phase | Whole cells—slight D,* slight R (eyelid margins only)<br>Broken cells—full |
| Early stationary phase, stored two days at 4°C (rewashed before use) | Whole cells—D, R, S (less than control<br>Broken cells—full |
| Early stationary phase, frozen | Whole cells—full<br>Broken cells—full |

* D, R, S: production of discharge, redness and swelling respectively in response to conjunctival instillation.

the type of oligosaccharides which would result from keratanase activity (i.e., β-acetylglucosaminidase and β-galactosidase) were found to be present in the cell extract. Lipase activity was detected on a tributyrin substrate. The lipase was not inactiviated by heating for three minutes at 55° C, but was completely inactivated by three minutes at 100° C. Since some toxic activity remains after this heat treatment, it would seem that the lipase probably does not play a major role in production of toxic effects.

Proteolytic activity, as measured by release of amino acids from casein or gelatin, was not detected in cell extracts. Bacteriologic tests for the hydrolysis of gelatin were also negative. However, a high level of peptidase activity was demonstrated on leucyl-glycyl-glycine. This enzymatic activity showed a heat sensitivity which paralleled that of the toxic factor, and thus it may be involved in the production of the toxic effects.

The pneumococcal extract contains an active hemolysin. The hemolysin does not appear to be involved in the production of toxic effects, as it was completely inactivated by heating for three minutes at 55° C, a procedure having no effect on toxic activity. We have attempted to measure phospholipase C activity on numerous substrates, as in some bacteria this enzyme is responsible for hemolytic activity. However, no phospholipase C activity was detected.

At present we are planning to fractionate the cell extract with gel filtration, column chromatography, and electrofocusing techniques and to follow toxic activity and the activity of the degradative enzymes in an attempt to correlate the two.

TABLE 3

DEGRADATIVE ACTIVITIES OF THE CELL EXTRACT

| Extract | Level of Activity | Observations |
|---|---|---|
| Mucopolysaccharases: | | |
| Hyaluronidase | SA* = 2.0 | Not inducible† |
| Chondroitinase | None | Not inducible† |
| Keratanase | None | Not inducible† |
| Other glycosidases: | | |
| β-acetylglucosaminidase | SA = 3.3 | Determinations made with cells grown to late exponential phase; activity lower in older cells |
| β-galactosidase | SA = 20.5 | |
| Lipase | 6 mm zone/2 hr/0.025 mg protein | Completely inactivated by heating three minutes at 100°C |
| Proteinase: | | |
| Diazocasein | None | |
| Gelatin | None | |
| Peptidase | SA = 20.1 | Retains 75% of activity after heating for three minutes at 100°C |
| Hemolysin | 2250 $HD_{50}$ per mg protein | Completely inactivated by heating three minutes at 55°C |
| Phospholipase C | None | |

* S.A. = μM/hour/mg protein.

† Enzyme activity not increased by addition of substrate (0.5%) to growth medium.

## SUMMARY

Extracts of a pneumococcus have been shown to produce a severe inflammatory reaction upon instillation into the rabbit eye. Upon intracorneal injection of the material, extensive corneal opacification was also observed. The toxic factor was shown to be non-dialyzable, trypsin-sensitive, and precipitable by ammonium sulfate, indicating that it is a protein. It is released from the cells upon aging or after freezing and thawing. A high level of hemolysin and various degradative enzyme activities have been demonstrated in the pneumococcal extract, including hyaluronidase, glycosidases, lipase, and exopeptidase. Only the exopeptidase showed a level of heat resistance comparable to that observed for the toxic factor.

## ACKNOWLEDGMENT

The keratosulfate used in this study was supplied by Dr. J. Anthony Cifonelli.

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OPHTHALMIC MINIATURE

Mr. Squeers's appearance was not prepossessing. He had but one eye and the popular prejudice runs in favour of two. The eye he had was unquestionably useful but decidedly not ornamental; being of a greenish grey, and in shape resembling the fanlight of a street door. The blank side of his face was much wrinkled and puckered up, which gave him a very sinister appearance, especially when he smiled, at which times his expression bordered closely on the villainous.

Charles Dickens
Nicholas Nickleby

# BACTERIAL PROTEASES IN MORAXELLA ANGULAR CONJUNCTIVITIS

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Biochemical activity of Moraxella species associated with infections of the outer eye is generally low and consequently it is not very surprising that early workers such as Petit[1] associated Moraxella proteases with virulence and pathogenicity. Paul,[2] Schmidt,[3] and Scarlett[4] made observations at variance with Petit's view which was largely abandoned.

It is generally accepted, however, that these bacterial enzymes are responsible for the characteristic angular maceration as postulated by Abe.[5] Only relatively recently, Thygeson and Kimura[6] challenged the concept of the overriding importance of Moraxella proteases in the causation of the angular lesion, and thus, in fact, also the hypothesis of Abe[5] on the explanation of the typical localization.

Angular conjunctivitis with strikingly large macerations was observed in two sisters with generalized ichthyosis. The observation was interesting in that from each patient a separate Moraxella species was isolated which differed markedly in proteolytic ability. It appeared that the extent and localization of the maceration was associated with quantity and position of the coherent exudate rather than the proteolytic ability of the strains.

## CASE REPORTS

Two sisters, patients A and B, aged 12 and 16 years, respectively, were referred to the Eye Clinic for treatment of intractable bilateral conjunctivitis. Both patients were inmates of separate wards in an institution for retarded children.

Upon examination, conjunctival hyperemia was found. It was most pronounced in the interpalpebral fissure. Gray coherent mucous exudate was present in quantity at the internal canthi, spreading onto the skin of the commissures. The most striking signs were the unusually large macerations of the skin, extending some 9 mm from the internal canthi. The configuration of the maceration was rather similar to the position of the exudate. The aspect of the inflammatory reaction of both eyes of both sisters was virtually identical.

Each had generalized ichthyosis which had resulted in moderate bilateral ectropion and disciform corneal changes. The normal configuration at the internal eyelid commissures was also altered.

Smears from the exudate revealed Gram-negative diplobacilli. From the discharge of both eyes of patient A, M. liquefaciens was cultured, while from the discharge of both eyes from patient B, a hitherto unrecognized carbohydrate-splitting Moraxella strain was isolated.[7] The strain was catalase-negative, nonhemolytic, produced indole and produced acid from a number of carbohydrates.

## DESCRIPTION OF NEW STRAIN

A short description of the new Moraxella strain follows:

*Micromorphology*—Medium-sized rods with rounded ends in pairs and chains (Fig. 1); Gram-negative; capsulated (Fig. 2); no flagellar motility, but "gliding" motility is present; no endospores.

*Colonies*—Translucent or slightly opaque, 0.15 to 0.5 mm in diameter after 24 hours. Colonies have low hemispheric or low conical elevation, with a tendency to differentiate into a raised center and flattened periphery. No beta hemolysis.

*Relation to oxygen*—Strictly aerobic.

*Temperature*—Optimal growth at 33° to 37°C; no growth initiated at 20°C.

*Growth requirements*—No growth in Koser's citrate medium and Audureau's medium. Very little growth in Hugh and Leifson's medium and peptone media. Growth enhanced by the addition of blood, serum, or ascites.

*Biochemical reactions*—Oxidase-positive, catalase-negative. Nitrate and nitrite were not reduced. Acid from glucose, fructose, mannose, saccharose; some acid was produced from starch, dextrine, and maltose. A trace reaction was found with galactose, trehalose, and xylose. Minimal gelatinase and proteolytic activity. Indole was produced.

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Fig. 1 (van Bijsterveld). The new Moraxella strain. Four-hour culture showing the spongy cytoplasm of the cells characteristic of Moraxella species (Bouin-thionin preparation, ×1750).

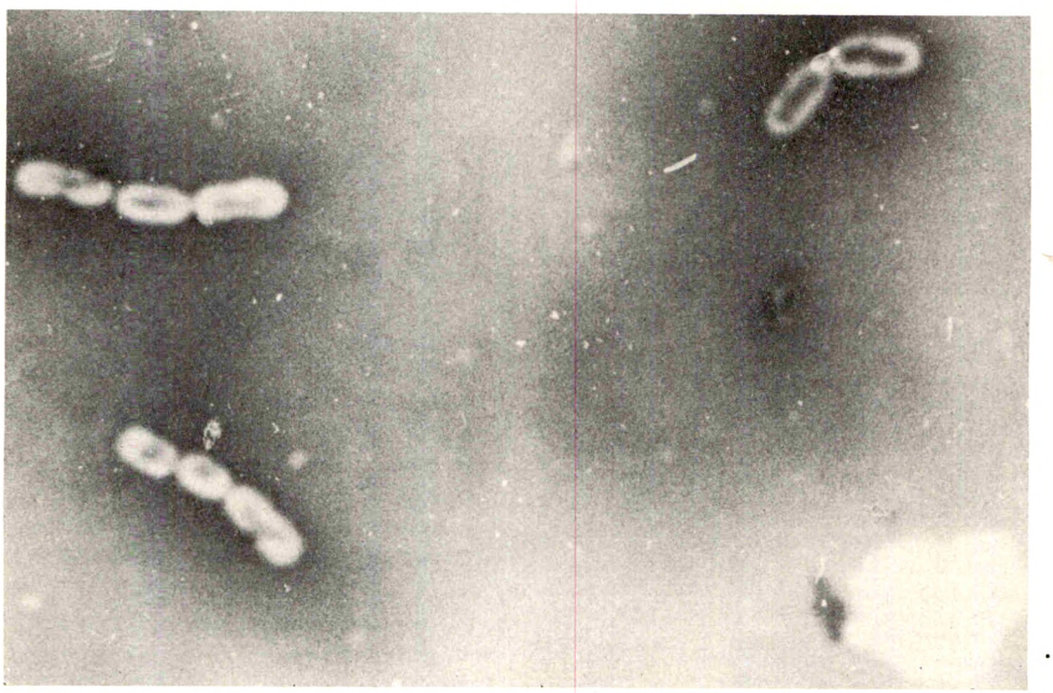


Fig. 2 (van Bijsterveld). Capsules of the new Moraxella strain (white capsule stain, ×4000).

$H_2S$ was not produced. No urease activity was found. The methyl red test was negative. Acetylmethylcarbinol was not produced. The phosphatase test was positive. Oxidative deamination of L-phenylalanine and DL-norleucine. Decarboxylase reactions are negative.

*Antibiotic sensitivity*—Highly sensitive for penicillin, streptomycin, chloramphenicol, oxytetracycline, erythromycin.

*DNA base composition*—Composed of 49 mole% guanine + cytosine (CsCl buoyant density method).

In Table 1 the differential characteristics of the carbohydrate splitting Moraxella species, i.e. M. amylolytica,[8] M. kingii,[9] and the new Moraxella strain are presented. It must be remembered that M. saccharolytica (Flamm, 1956[10]) has been identified as Flavobacterium meningosepticum.[11]

The species isolated from our patients differed markedly in their proteolytic activity. While M. liquefaciens produced powerful proteases, liquefaction of serum by the carbohydrate-splitting Moraxella could be demonstrated with difficulty. Likewise, gelatinase activity was minimal but could be detected by incorporating 3% w/v gelatine in the Moraxella base medium[12] and treatment of the surface of the medium with saturated ammonium sulfate after a suitable time of incubation.

TABLE 1

DIFFERENTIAL CHARACTERISTICS OF THE CARBOHYDRATE-SPLITTING MORAXELLA SPECIES

| Determination | M. amylolytica | M. kingii | New Moraxella Strain |
|---|---|---|---|
| Catalase production | + | − | − |
| Serum liquefaction | − | − | (+)* |
| Gelatin liquefaction | + | − | (+) |
| Beta hemolysis | − | + | −† |
| Indole production | + | − | + |
| Acid from saccharose | − | − | + |
| Acid from fructose | − | − | + |

* Weak reaction.

† Beta hemolysis only with the 1-mm rabbit blood agar overlay medium.

## DISCUSSION

While relatively little attention has been given to host factors in the causation of Moraxella infection, there has always been much interest in the offensive powers of these conditional pathogens for which the bacterial proteases were thought to be responsible.

Since the isolation of M. lacunata and M. nonliquefaciens from corneal ulcers, the concept of the relation of virulence and pathogenicity to qualitative and quantitative differences in proteolytic enzymes became untenable. The role of bacterial proteases in the causation of angular lesions is still generally accepted. However, Thygeson and Kimura[6] reported the isolation of M. nonliquefaciens from cases of angular conjunctivitis that were clinically in no way different from those associated with proteolytic Moraxella. Also, proteases are very common with microorganisms associated with infections of the outer eye and even with members of the normal conjunctival flora. It is difficult to see why these macerations would not occur more often in conjunctivitis if bacterial proteases alone were responsible.

The localization of the macerations in Moraxella angular conjunctivitis was explained by the unfavorable ratio of the supposedly protective antiproteolytic tear enzymes and bacterial proteases at the canthi. Since tears tend to collect at the angles this explanation seems unlikely to begin with.

We have isolated M. lacunata, M. liquefaciens, M. nonliquefaciens and a carbohydrate-splitting Moraxella species from angular conjunctivitis. Even in the infections caused by the proteolytic species, we did not find a correlation between the amount or type of proteases and size or location of the maceration, which was rather clearly exemplified in two of our two patients with ichthyosis.

One common denominator, however, in all those infections was the typical Moraxella exudate with its predilection to accumulate at the angles. It is the combination of the co-

hering and adhering quality of the exudate and the chronicity of the infection that distinguishes Moraxella infections from mucopurulent infections caused by other organisms.

Ichthyosis had changed the natural barrier of the eyelid folds at the internal canthi in our patients, facilitating the spread of the exudate well onto the skin at the commissures. The configuration of the macerated areas in our patients was rather similar to the extension pattern of the exudate. It seems much more likely that the size and the typical localization of the maceration is conditioned by contact of the skin with the exudate, rich both in bacterial and host metabolic products, including proteases from the inflammatory cells, rather than the interaction of bacterial proteases and protective antiproteolytic enzymes of the tears.

## Summary

Two Moraxella species, M. liquefaciens and a new carbohydrate-splitting Moraxella species that differed markedly in proteolytic activity were isolated from the exudate of two patients, sisters, with angular conjunctivitis characterized by large macerations. Generalized ichthyosis had changed the configurations of the canthi, allowing the exudate to spread onto the skin. The extent of the maceration and its localization appeared closely related to the position of the exudate.

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# GNATHOSTOMA SPINIGERUM: AN UNUSUAL CAUSE OF OCULAR NEMATODIASIS IN THE WESTERN HEMISPHERE

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According to Sirisamban,[1] the first reported case of ocular gnathostomiasis was recorded in Thailand in 1936. He reported the second case in 1941 and alluded to two others which he had seen but had not reported. Neither of these reports has been previously cited in the Western ophthalmic literature. Six cases (eight reports[2-9]) of ocular gnathostomiasis have been well documented in the Western literature prior to this paper. Two more cases have recently been reported from India.[10]

The present case is reported not only because of its rarity, but also because it is unique in two respects: it is the second to be diagnosed in the western hemisphere, and it has been possible to establish with certainty that a minimum time of three and one-half years elapsed between ingestion of the worm and the appearance of clinical disease.

## CASE REPORT

The patient, a 17-year-old, single, Filipino girl left Bocarra Ilorcas Norte, Luzon, in August, 1966. She visited relatives in Oahu and Maui, Hawaii, on her way to the continental United States. She has lived in Southern California since her arrival in September, 1966. In the Philippines she ate raw fresh-water shrimp prepared in a dish called "udang," fresh water fish called bañgos, and the "walking catfish" (Clarias batrachus).

On the evening of March 21, 1970, a dark spot, which moved, appeared in the visual field of the left eye. The patient awakened the following morning with decreased vision, redness and pain of the left eye. Finding no spontaneous improvement over the subsequent two days, she presented herself with these complaints on March 24, 1970.

Ocular examination revealed the right eye was free of disease and possessed 20/20 vision without correction. Vision in the left eye was counting fingers at three feet. The left eye demonstrated the signs of a severe uveitis: marked conjunctival hyperemia and ciliary flush, a blood-tinged hypopyon occupying the lower one-third of the anterior chamber, plasmoid aqueous superior to the hypopyon, and myriad red and white blood cell keratic precipitates. The pupil was round and regular and 6.0 mm in diameter. It reacted sluggishly and incompletely to direct and consensual light and accommodative stimuli. No synechiae were present. The lens and vitreous were clear. A choroidal and subretinal hemorrhage four disk diameters in width was present one disk diameter superior temporal to the optic nerve head. A retinal tear was present in the area of hemorrhage, and preretinal and vitreous blood, which partially obscured the disk, had come from this source (Fig. 1). We believe the worm entered the eye at this point by boring through the sclera, choroid, and retina from the orbit.[11]

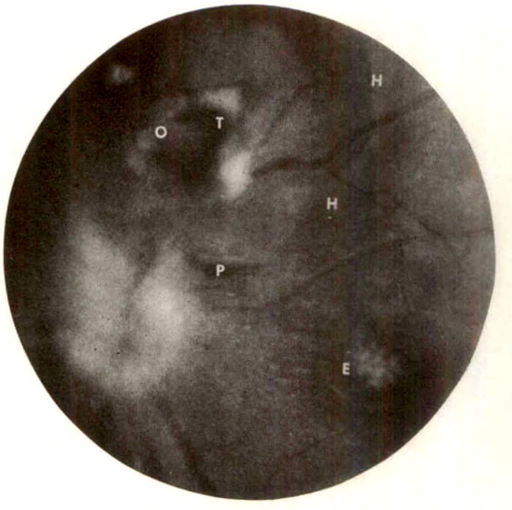



Fig. 1 (Tudor and Blair). Fundus photograph of the left eye taken six days after the onset of the patient's first symptoms. O = operculum of the retinal tear, T. H indicates the perimeter of the choroidal and subretinal hemorrhages. P marks the preretinal hemorrhage. E = macular exudate which developed six days after the onset of symptoms. The appearance of the fundus is otherwise unchanged from the time of the initial examination.

A 1.0% atropine ointment and 10.0% phenylephrine drops were instilled into the patient's eye. She was given prednisolone acetate 1.0% ophthalmic drops to place into the eye at hourly intervals and was instructed to return the following day. At 1 P.M. on

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Fig. 2 (Tudor and Blair). The worm in the anterior chamber at surgery. The S-shaped form of the nematode is visible overlying the pupil and the 12 o'clock meridian of the iris.

March 26, the vision remained unchanged. The inflammatory response was markedly decreased and the hypopyon had disappeared almost completely. The plasmoid aqueous persisted. A red, immobile nematode was seen lying in the angle between five and seven o'clock. It floated about the anterior chamber when the patient's posture was changed.

The patient was admitted and a complete history was taken and a physical examination was performed by the patient's internist. No signs or symptoms of systemic disease were found.

By 7 P.M. on March 26, the patient was prepared for surgery and photographs were taken (Fig. 2). The worm was actively moving at this time. The globe was fixated and a keratome incision was made through the cornea at the anterior edge of the temporal limbus. A lacrimal cannula attached to a 5 ml syringe filled with sterile lactated Ringer's solution was introduced into the anterior chamber through the keratome incision, and one end of the actively moving worm was aspirated into the cannula. The entire nematode was withdrawn from the eye. A single 7-0 silk suture was used to close the keratome incision; 2 mg of dexamethasone in 0.5 ml of diluent were injected subconjunctivally over the inferior portion of the globe at the conclusion of surgery. After 1.0% atropine ointment and corticosteroid (Cortisporin) ointment were instilled into the eye, a patch and shield were applied.

The patient's postoperative course was uneventful. The following points were of interest: two highly refractile, fine white strands looking like mucus were noted on the iris near the keratome incision on March 27. These strands disappeared as the inflammatory response in the anterior chamber diminished. We believe them to have been secretions from the parasite. By March 30, the visual acuity was correctable to 20/50. A +4 cellular reaction was present in the anterior chamber at this time. When examined on April 1, the patient complained of decreasing visual acuity, and a yellow exudate was seen in the macular area for the first time. By April 6, the best corrected vision was 20/100, but the yellow macular exudate had completely cleared leaving only a small degree of macular edema. There were +2 cells in the anterior chamber at this time. The patient was continued on prednisolone acetate 1.0% four times daily, and on April 14 the anterior chamber contained only an occasional cell, the vision was 20/50 with −1.25 sph. ⊃ −1.00 cyl. ax. 10, and gliosis had occurred in the area of the choroidal and subretinal hemorrhage. A few folds of the internal limiting membrane of the retina were present.

Complete blood counts performed on March 24 and 26 showed 75 and 85% polymorphonuclear leukocytes and 4 and 2% eosinophils, respectively. The corrected sedimentation rate was 26 mm/hour. These were the only abnormal or borderline laboratory test results. Three stool examinations for ova and parasites were negative and three blood smears were negative for microfilaria. Immunoelectrophoresis and special procedures for the determination of IgE were performed and were normal.

The patient disappeared from follow-up between April 1 and June 25. On June 25 the best corrected vision was 20/20 in the right and counting fingers at one foot in the left eye. Fibrous tissue bands extended from the worm's point of entrance into and

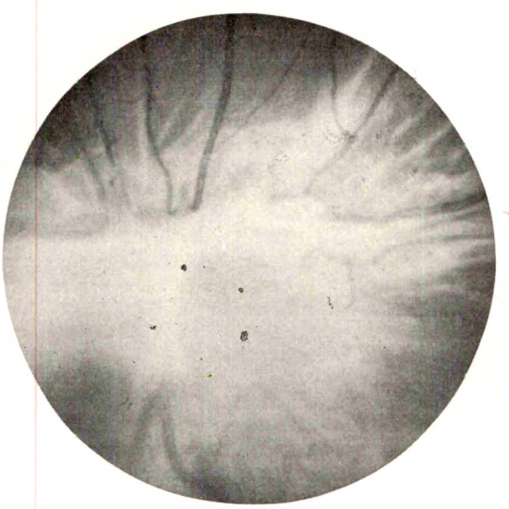


Fig. 3 (Tudor and Blair). Fundus photographs of the left eye three months after the onset of first symptoms. Same field of view as Figure 1. The fibrous bands outlining the course of the worm through the vitreous and the retinal detachment produced by their traction on the retina are clearly seen. The bands originate and terminate at points where the worm contacted the retina.

through the vitreous, outlining the path which the worm had traversed. Contraction of these fibrous bands had produced total detachment of the retina (Fig. 3). We think that excretions of the worm produced this reaction.

## Discussion

The nematode genus, Gnathostoma, was first described and named by Richard Owen in 1836 when he found the worm in a tumor of the stomach wall of a tiger which had died in the London Zoological Gardens.[12] At the present time approximately 20 species of Gnathostoma have been described.[13] Of these species, only three, with certainty, have been found as the cause of human gnathostomiasis: G. spinigerum, G. hispidum, and G. viverrina.[14] These species are found primarily in Southeast Asia and in the Japanese, Philippine, and Indonesian archipelagoes. G. spinigerum is by far the most common cause of human infection and was the worm removed from the eye of our patient.[15]

While alive, the worm was red-orange in color and measured approximately 4.5 mm long by 0.5 mm wide. The color comes from oxyhemoglobin retained in solution in the worm's body fluids.[16] The head bulb had four rows of hooklets. From the most anterior row to the most posterior row the minimum numbers of hooklets in each row, were respectively: 27, 33, 40, and 48. A precise hooklet count was not possible since they could only be counted from lateral view. Spination of the body was prominent over its anterior half but the single, pointed 10μ-long spines became shorter posteriorly until they were ultimately lacking on the posterior fourth of the body. The morphologic characters of the larva are consistent with a diagnosis of G. spinigerum.[13]

Gnathostomes can infect all human soft tissues. As a result, the signs and symptoms of human gnathostomiasis are protean and depend, in the individual case, upon the random migration of the larva through the host tissues. Most commonly, human gnathostomiasis is observed as a cutaneous larva migrans. Rangoon tumor (Burma), Embassy

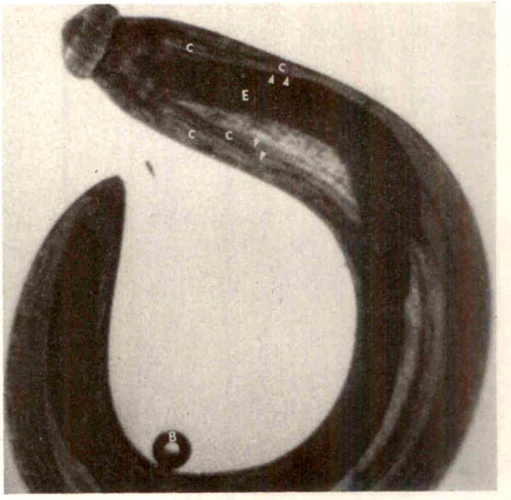



Fig. 4 (Tudor and Blair). Photomicrograph of the third-stage larva in life. Note the well-defined head with its four rows of hooklets and the transverse striations of the body. These striations are composed of single pointed spines which are 10 μ long anteriorly but which diminish in length until they disappear posteriorly. Also note the well-defined divisions of the alimentary tract. Lying alongside the anterior portion of the esophagus, E, are four muscular tubes called the cervical sacs, C, which play an important role in swelling and contraction of the head bulb. The arrows indicate the posterior edges of the cervical sacs. B is an air bubble.

disease, or Yangtze river edema, consulate disease (Nanking), and Shanghai rheumatism are some of the local names used to describe a cutaneous larva migrans which may be caused by gnathostomes.[17,18] Less commonly, disease of the CNS, eyes, lungs and pleura, urinary tract, intestines, mastoid sinuses and uterus has been reported as having been caused by the larvae of gnathostomes.[11,15,19-22] Congenital infection of the newborn is also known to occur.[23]

Since G. spinigerum was reported for the first time in 1889 as a cause of human disease—producing a breast abscess in a Siamese woman—human infection with gnathostomes has been reported with increasing frequency.[24] Subsequently most human cases have been reported from Thailand and Japan, although human gnathostomiasis has also been reported in Malaysia, Burma,

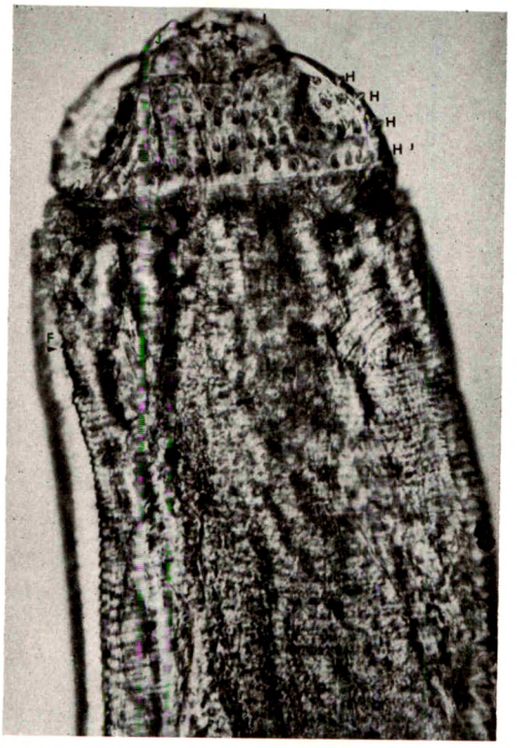



Fig. 5 (Tudor and Blair). Photomicrograph of the head and anterior body of the third-stage larva after fixation in formalin. Numerous artifacts have been created by the shrinkage produced by this fixative; 70% ethanol containing 5% glycerin and warmed to the vapor point is the proper fixative for nematodes. J = the massive labia about the mouth which give the genus its name. H = the four rows of hooklets on the head bulb. The minimum counts for each of the four rows in the pictured specimen were 27, 33, 40, and 48, respectively. F = one of the fine body hooklets seen highlighted against a diffraction image produced by the thickness of the specimen.

Vietnam, China, India, Pakistan, the Philippines, Israel, and North Queensland, Australia. In Thailand the infection is so commonly recognized as not to warrant reporting of individual cases.

The life cycle of the gnathostomes is quite complex. Daengsvang has elucidated the cycle.[15,23,25,26] During the three larval stages, the parasite lives first in fresh water, then successively in two intermediate hosts (copepods and cold-blooded vertebrates), and finally reaches maturity in the definitive host. The adult worms produce eggs which are passed in the host's feces to begin the cycle again.

The known natural definitive hosts of G. spinigerum include wild and domestic felines and dogs. The adult male and female worms cohabit in tumors of the stomach wall and eggs are layed in the lumen of the host's gut via a small opening at the mucosal surface of the tumor. Eggs develop and hatch about one week after entering fresh water. Free-swimming, first-stage larvae emerge and die unless ingested by one of several species of cyclops, a fresh water crustacean (copepod), within two or three days. If ingested, the first-stage larvae penetrate into the body cavity of the copepod, molt twice, and in approximately one week become third-stage larvae (Figs. 4 and 5). Fish, snakes, or frogs eat the copepod and the larvae migrate from the intestinal tract of these animals into their muscles where they become encapsulated. If these infected second intermediate hosts are eaten by another animal capable of serving as a second intermediate host for the worm, the worm re-encapsulates without further development. When the definitive host eats the second intermediate host, the third-stage larvae penetrate the walls of the stomach or duodenum, migrate into the host's liver, muscles, and connective tissues, molt twice and then return to the wall of the stomach where they mature and produce the characteristic nodules.

Man is an abnormal host for gnathostomes. The third-stage larvae undergo their characteristic tissue migration but cannot reach maturity in man. The larvae may wander aimlessly into all parts of the body. As they bore through the tissues they sometimes produce the signs and symptoms of clinical disease—although we have seen how they may also move about without symptoms. They fail to return to the stomach as mature adult worms, and the ova-producing nodules of the upper GI tract do not develop. Thus humans are not considered to be infective even when harboring worms.

The question of the mode of human infection has often been discussed. There are two

possible ways in which the mammalian host can be infected. The most common is by the ingestion of the infected second intermediate host. A rare means of infection can be by the ingestion of infected copepods in drinking water. This has been experimentally demonstrated in pigs and has been suggested to occur in G. procyonis infections.[27,28] However, human infection is more often acquired by eating raw or improperly cooked fish, either through carelessness or through choice. There is no experimental evidence that infection can occur through the skin.

The diagnosis of human gnathostomiasis can be made only by removal and morphologic identification of the larvae. An eosinophilia or elevation of sedimentation rate is more often absent than present in gnathostomiasis.[29]

In every reported case of ocular gnathostomiasis in which the time of onset of symptoms has been mentioned, it has been in the evening. The increased motility of the worm noted by us at surgery may explain this phenomenon.

## Summary

A 17-year-old Philippine girl suddenly developed a severe uveitis of the left eye three and one-half years after leaving Luzon. The uveitis was caused by a third stage larva of Gnathostoma spinigerum which had entered the globe by boring through the sclera, choroid, and retina superior to the optic disk, traversing the vitreous, entering the anterior chamber after penetrating the ciliary body and iris. The larva was successfully removed by aspiration and vision returned to 20/50 four days postoperatively only to be reduced to light perception three months later when fibrous bands that formed along the path traveled by the worm through the vitreous contracted and produced retinal detachment. No systemic signs or symptoms of parasitic infection were apparent in the patient.

This is the second case of ocular gnathostomiasis reported from the Western hemisphere and is interesting because it developed three and one-half years after the patient's last exposure to a source of infection.

*Addendum:* Since this paper was submitted for publication, a report of two human gnathostome infections in native-born Mexicans, who had never left their country, has come to our attention. One of these infections was ocular (diagnosed in 1967 by Dr. E. López-Quiñones of Mexico City) and the other involved the abdominal wall. Species identification was not possible in these two cases. This report antedates ours and accordingly describes the first known cases of human gnathostomiasis in the western hemisphere.[30]

### Acknowledgment

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# EVALUATION OF 48 CASES OF ORBITAL EXENTERATION

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Orbital exenteration is a radical surgical procedure. It must, however, be done when less radical operations, local chemosurgery, or irradiation will not eradicate malignant tumors of the orbit or periorbital tissues. A critical review of the literature reveals little information on results of orbital exenterations. Naquin[1] reported 48 orbital exenterations performed at the Wilmer Ophthalmological Institute; Simons and associates[2] presented follow-up data on 31 patients who had undergone exenteration for malignant orbital and periorbital tumors; and Jones and Reese[3] reported on rhabdomyosarcoma treated with exenteration, irradiation, or both. In order to further assess the value of orbital exenteration and to determine which types of tumors respond best to this radical surgery, all orbital exenterations done on both the private and clinic services at the University of California, San Francisco, were extensively evaluated and are reported here. Each tumor type was examined separately, since each has individual characteristics of growth rate, recurrence, type of spread, and of response to other modalities used in place of or in conjunction with orbital exenteration.

## Clinical data

Between 1940 and the present, 48 orbital exenterations were done within the Department of Ophthalmology of the University of California, San Francisco. Full descriptions of the operative techniques have been reported elsewhere.[4-6] Basically, the orbital contents and periosteum were removed in each case; the amount of eyelid skin excised varied with the location and extent of the tumor. Grossly involved bone was removed by rongeur until bone of normal consistency was encountered. The area of resected bone and the orbital apex were treated with electrocautery. Frontal, ethmoid, and maxillary sinuses were removed as necessary. A split-thickness skin graft from the thigh was used to line the orbital defect in 43 patients; temporalis muscle flaps were used in the remaining five. Radiation therapy, chemosurgery, or the two together were used postoperatively if indicated. Recurrences were treated by operation, or by irradiation and chemosurgery alone or combined.

*Basal cell carcinoma*—Orbital exenterations were done for advanced basal cell carcinoma in 14 patients (Table 1). Frontal, ethmoid, and/or maxillary sinuses were also exenterated in seven of the patients. Eleven of the patients were men; the average age at time of operation was 62 years (range: 23 to 82 years). The known duration of the carcinoma prior to operation ranged from one to 25 years. All but two of the tumors had been treated with surgical, chemical, or radiation therapy prior to exenteration.

Four patients are alive after five years of follow-up without recurrence; one died after more than five tumor-free years. Two patients, aged 38 and 44 years at the time of exenteration, survived five years but died of tumor recurrence seven years and nine years, 10 months, respectively, after exenteration. The latter had had two additional operations for recurrence of bony tumor invasion. Four patients are living without recurrent disease one and one-half to five years after exenteration. Three patients died in less than five years of causes that were not tumor related.

*Squamous cell carcinoma*—Of six cases of advanced squamous cell carcinoma, three originated from the conjunctiva, two from

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TABLE 1

DATA FROM 14 PATIENTS UNDERGOING ORBITAL EXENTERATION FOR BASAL CELL CARCINOMA

| Case No., Age, and Sex | Eye Removed | Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 1. 71-M | Left | Basal cell carcinoma of left medial canthus extending into orbit, ×9 years | No | No | Died with intracranial hemorrhage 4 years 5 months, tumor-free | |
| 2. 77-M | Left | Basal cell carcinoma upper eyelid and medial canthus involving tear sac, ×22 years | No | No | Died of cerebral hemorrhage 5 years 1 month, tumor-free | |
| 3. 44-F | Left | Basal cell carcinoma upper eyelid with involvement of superior orbital nerve, ×6 years | No | No | Died 9 years 10 months with tumor probably present | Reoperations in 1946 and 1953 for recurrent tumor of frontal and zygomatic bones |
| 4. 77-M | Right | Basal cell carcinoma upper eyelid, ×4 years | No | No | Died tumor-free at 2 months of uremia and pneumonia | |
| 5. 23-M | Left | Basal cell carcinoma lower eyelid and orbit, ×6 years | Yes | Yes | Alive 16 years tumor-free | Reoperations 1956 and 1959 for recurrence in orbital roof, tumor-free, ×10 years |
| 6. 74-M | Left | Basal cell carcinoma lower eyelid, ×8 years | No | No | Died at 9 months of cardiac disease, tumor-free | |
| 7. 38-F | Left | Basal cell carcinoma of inner canthus and orbit with eye fixed to inferior orbital rim, ×14 years | No | No | Died 7 years with intracranial extension | Maxillary and ethmoid sinuses exenterated |
| 8. 61-M | Left | Basal cell carcinoma lower eyelid, ×6 years | Yes | No | Alive 7½ years, tumor-free | Frontal and maxillary sinuses exenterated |
| 9. 82-M | Right | Basal cell carcinoma lower eyelid and orbit, ×7 years | No | No | Alive at 6 years, tumor-free | Exenteration of ethmoid and sphenoid sinuses |
| 10. 75-M | Right | Basal cell carcinoma lateral canthus extending into orbit, ×1+year | No | No | Alive 5 years, 9 months, tumor-free | Maxillary sinus, lateral orbital wall, orbital floor, and zygomatic arch removed |
| 11. 59-M | Left | Basal cell carcinoma lower eyelid and orbit, ×6 years | No | No | Alive 4 years, 5 months, tumor-free | Medial orbital wall, ethmoid and frontal sinuses removed |
| 12. 53-M | Left | Basal cell carcinoma lower eyelid and orbit, ×4 years | No | No | Alive 2 years, 5 months, tumor-free | |

TABLE 1 (*Cont'd*)

| Case No., Age, and Sex | Eye Removed | Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 13. 65-M | Left | Basal cell carcinoma lower eyelid, orbit, and inferior orbital rim, ×25 years | Yes | No | Alive 1 year, 5 months, tumor-free | Inferior orbital rim, maxillary and ethmoid sinuses removed |
| 14. 73-F | Left | Basal cell carcinoma inner canthus and orbit, ×1+year | No | Yes | Alive 1 year, tumor-free | Frontal, maxillary and ethmoid sinuses removed |

the eyelid skin, and one from the tear sac (Table 2). The patients' ages ranged from 61 to 77 years.

The three patients with squamous cell carcinoma of the conjunctiva are tumor-free after five months, six and one-half years, and 13 years, respectively. The two patients whose initial lesion was in the eyelid skin died of causes unrelated to their tumor at 21 months and seven years, five months, respectively. The patient whose primary tumor had originated in the tear sac died of accidental causes one year, nine months, postoperatively. None of these patients required any further surgical or radiation therapy.

*Melanoma*—Eight patients underwent

TABLE 2

DATA FROM SIX PATIENTS UNDERGOING ORBITAL EXENTERATION FOR SQUAMOUS CELL CARCINOMA

| Case No., Age, and Sex | Eye Removed | Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 15. 76-F | Right | Squamous cell carcinoma of lower eyelid invading orbit, ×40 years | No | No | Died of myocardial infarction at 21 months tumor-free | |
| 16. 73-M | Right | Squamous cell carcinoma of tear sac, ×1½ years | No | No | Accidental death 1 year, 9 months, tumor-free | |
| 17. 60-M | Right | Squamous cell carcinoma of conjunctiva, ×4 years | No | No | Alive 13½ years, tumor-free | |
| 18. 77-M | Right | Squamous cell carcinoma upper eyelid, ×2+years | No | No | Died of pneumonia 7 years, 5 months, tumor-free | |
| 19. 76-M | Left | Squamous cell carcinoma of conjunctiva, ×2 years | No | No | Alive 6½ years, tumor-free | |
| 20. 61-M | Left | Squamous cell carcinoma of conjunctiva, ×15 months | No | No | Alive 7 months, tumor-free | |

TABLE 3

DATA FROM EIGHT PATIENTS UNDERGOING ORBITAL EXENTERATION FOR MELANOMA

| Case No., Age, and Sex | Eye Removed | Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 21. 58-F | Left | Melanoma of conjunctiva, 3 large nodules in lower fornix, ×3+ months | No | No | Last seen 9 years postoperation, tumor-free | |
| 22. 79-F | Left | Melanoma of conjunctiva, ×6 years | No | No | Died of heart disease 5 years, 6 months, tumor-free | |
| 23. 29-F | Left | Melanoma of conjunctiva, ×4 years | No | No | Died of metastases 4 years, 10 months | |
| 24. 48-F | Right | Melanoma of conjunctiva, ×5 months | Yes | No | Died of metastases 3 years, 9 months | |
| 25. 50-M | Right | Melanoma of conjunctiva, ×1 year | No | No | Accidental death at 14 months, tumor-free | |
| 26. 58-F | Right | Choroidal melanoma extending into orbit | No | No | Alive 19 years, tumor-free | |
| 27. 60-F | Right | Choroidal melanoma with extensive orbital involvement, ×4 years | No | No | Died of metastases, 10 years | Maxillary sinusectomy and cautery to remaining tumor in superior and inferior orbital fissures |
| 28. 38-F | Right | Melanoma of orbit with history of excision of melanoma of arm 7 years before | No | No | Died of metastases, 6 months | |

orbital exenteration for malignant melanoma (Table 3). This originated in the conjunctiva in five patients, the choroid in two patients, and the orbit in one patient in whom the tumor was possibly related to a skin melanoma excised from the arm seven years before. The average age of these patients was 52.5 years (range: 29 to 79 years); seven of the eight were women.

Of the patients with conjunctival melanoma: two died of metastatic tumor at three years, nine months, and four years, ten months, respectively; one died accidentally at 14 months; one is alive after nine years without recurrence; and one died five years, six months, postoperatively, apparently free of melanoma. One patient with advanced orbital involvement from choroidal melanoma died of metastatic disease 10 years later; the remaining patient with choroidal melanoma is alive with cure 19 years after operation. The patient with orbital melanoma died six months postexenteration of metastatic disease.

*Rhabdomyosarcoma*—Five patients, aged one and one-half to six years (average four and one-third years), underwent orbital exenteration for rhabdomyosarcoma, followed by irradiation in three (Table 4). One patient died of cardiac arrest two hours postoperatively. One patient (irradiated) died of tumor at nine months, while two are alive without recurrence at nine and one-half years and 13 years (irradiated). One patient

TABLE 4

DATA FROM 5 PATIENTS UNDERGOING ORBITAL EXENTERATION FOR RHABDOMYOSARCOMA

| Case No., Age, and Sex | Eye Removed | Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 29. 6-M | Left | Rhabdomyosarcoma ×2 weeks | Yes | No | Alive 13 yr, tumor free | — |
| 30. 1½-F | Left | Rhabdomyosarcoma ×6 months | Yes | No | Died 9 months of extensive intracranial involvement | — |
| 31. 5-F | Right | Rhabdomyosarcoma ×6 weeks | No | No | Alive 9½ year, tumor free | — |
| 32. 3-M | Right | Rhabdomyosarcoma ×1 month | No | No | Died 2 hours, postoperatively of cardiac arrest | — |
| 33. 6-M | Left | Rhabdomysarcoma ×3 weeks | Yes | No | Alive 2 years, 10 months, tumor free | Reoperated for recurrence 8½ month postexenteration |

with recurrence discovered nine months after operation is alive two years and 10 months postexenteration, apparently tumor-free after a course of radiation therapy.

*Lacrimal gland tumors*—Of eight orbital lacrimal gland tumors leading to orbital exenteration, five were adenocarcinomas and two were mixed tumors (Table 5). One, on frozen section, was misdiagnosed as adenocarcinoma, while permanent sections showed lymphosarcoma. One accessory lacrimal gland tumor was an adenocarcinoma. The patients ranged in age from 22 to 80 years (average, 58 years).

Of the five patients with adenocarcinoma of the orbital portion of the lacrimal gland: three died at 12 months, 15 months, and 24 months postexenteration of metastatic disease; one died of accidental causes 10 months postoperatively with recurrent tumor present; and the fifth is alive seven months postexenteration. Two of these five patients had extensive resection of involved bone. The patient whose adenocarcinoma had originated in an accessory lacrimal gland developed cervical lymph node metastases two years and four months postoperatively; treatment was with irradiation followed by neck dissection. He died three years and 10 months postexenteration of cardiac disease. One patient with mixed tumor had no recurrence after three years while the other was treated with chemosurgery for recurrence four months postoperatively and is alive with no further recurrence at four years and two months after operation. The latter patient had had frontal and maxillary sinusectomies at the time of orbital exenteration. The patient with a final diagnosis of lymphosarcoma underwent radiation therapy postoperatively and died tumor-free eight years postexenteration.

*Other orbital tumors*—Six patients presented with other types of orbital tumors (Table 6): sarcomatous tumor (four patients); benign, rapidly growing granulomatous inflammation (one patient); and sebaceous-gland carcinoma of the upper and lower eyelids (one patient). Their ages ranged from 15 months to 82 years.

Three of the four patients with sarcomatous tumors are alive five years and three months, 17 years, and 23 years postoperatively. The fourth died of tumor 22 months postexenteration. The one patient with sebaceous-gland carcinoma died seven months postoperatively from a probably primary lung tumor. One patient underwent exenter-

TABLE 5

DATA FROM NINE PATIENTS UNDERGOING ORBITAL EXENTERATION FOR LACRIMAL GLAND TUMORS

| Case No., Age, and Sex | Eye Removed | Type and Site of Tumor and Duration Prior to Exenteration | Postex-enteration Radiation | Postex-enteration Chemo-surgery | Results | Comment |
|---|---|---|---|---|---|---|
| 34. 60-F | Left | Anaplastic carcinoma of orbit originating from lacrimal gland, ×3 weeks | Yes | No | Died of metastases at 2 years | |
| 35. 22-F | Left | Adenocarcinoma of lacrimal gland, extensive orbital involvement, ×4 years | No | No | Died with metastases at 15 months | Superior and lateral orbital walls resected |
| 36. 76-F | Right | Lymphosarcoma of lacrimal gland, ×6 months | Yes | No | Died of pneumonia 8 years, tumor-free | |
| 37. 67-M | Left | Malignant mixed tumor of lacrimal gland, ×2 years | No | No | Last seen 3 years postoperation, tumor-free | |
| 38. 44-M | Left | Malignant mixed tumor of lacrimal gland-"benign mixed tumor" excised 20 years before | No | Yes | Alive 4 years, 2 months, tumor-free | Maxillary and frontal sinusectomies. Recurrence at 4 months treated with chemotherapy |
| 39. 58-M | Left | Adenocarcinoma of accessory lacrimal gland, ×7 months | No | No | Died 3 years, 10 months cardiac disease, tumor-free | Cervical node metastases. Neck dissection done 2½ years later |
| 40. 59-F | Right | Adenocarcinoma of lacrimal gland, ×6 months | Yes | No | Died of metastases at 1 year | |
| 41. 80-F | Left | Adenocarcinoma of lacrimal gland, ×2 years | Yes | Yes | Died accidentally, 10 months, with recurrent tumor | |
| 42. 60-M | Left | Adenocarcinoma of lacrimal gland, ×2 months | Yes | No | Alive 6 months, tumor-free | Lateral orbital wall and part of sphenoid bone excised |

ation after multiple surgical procedures and irradiation had failed to control what was diagnosed microscopically as benign granulomatous inflammation. She died eight months postexenteration in another hospital with extensive pulmonary infiltration. An autopsy was not permitted.

## DISCUSSION

The compiled data by disease entity are presented in Table 7. While it is difficult to form conclusions from relatively small numbers of advanced tumor cases, it is our impression that orbital exenteration is a necessary and valuable procedure used either alone or in conjunction with radiation therapy and possibly local chemosurgery. Systemic chemotherapy was not administered to any patient in this series though consultation regarding its use was obtained in several cases.

In basal cell carcinoma, the results appeared to be good when all involved tissue and bone was removed. Twelve of our 14 pa-

TABLE 6

DATA FROM SIX PATIENTS UNDERGOING ORBITAL EXENTERATION FOR MISCELLANEOUS TUMORS

| Case No., Age, and Sex | Eye Removed | Type and Site of Tumor and Duration Prior to Exenteration | Postexenteration Radiation | Postexenteration Chemosurgery | Results | Comment |
|---|---|---|---|---|---|---|
| 43. 35-F | Left | Fibromyxosarcoma of orbit, ×1 year | No | No | Alive 23 years, tumor-free | |
| 44. 56-F | Right | Benign, rapidly growing granulomatous inflammation, ×7 months | No | No | Died 8 months with lung infiltrations, no autopsy | Ethmoids and maxillary sinuses removed |
| 45. 9-M | Left | Sarcoma of orbit, ×3 months | No | No | Died 22 months of tumor extension | |
| 46. 29-M | Left | Fibrosarcoma of orbit with infiltration of inferior and lateral orbital walls, ×2 years | No | No | Alive 17 years, tumor-free | Orbital floor and ethmoids removed |
| 47. 15 month-F | Left | Undifferentiated sarcoma of orbit, ×5 weeks | Yes | No | Alive 5 years, 3 months, tumor-free | |
| 48. 82-M | Left | Sebaceous gland carcinoma upper and lower eyelids, ×2 months | No | No | Died of probably primary lung tumor, 7 months | |

TABLE 7

SUMMARY OF DATA FROM 48 PATIENTS UNDERGOING ORBITAL EXENTERATION FOR TUMOR

| Disease | Total No. Patients | Alive at Less than Five Years' Follow-up | Dead at Less than Five Years | | Five-Year Survivals | |
|---|---|---|---|---|---|---|
| | | | Nontumor Deaths | Tumor Deaths | No Recurrence | With Recurrence |
| Basal cell carcinoma | 14 | 4 | 3 | | 5* | 2 |
| Squamous cell carcinoma | | | | | | |
| conjunctiva | 3 | 1 | | | 2 | |
| skin | 2 | | 1 | | 1* | |
| tear sac | 1 | | 1 | | | |
| Melanoma | | | | | | |
| conjunctiva | 5 | | 1 | 2 | 2* | |
| choroid | 2 | | | | 1 | 1 |
| orbit | 1 | | | 1 | | |
| Rhabdomyosarcoma | 5 | 1 | 1 | 1 | 2 | |
| Lacrimal gland | | | | | | |
| malignant mixed tumor | 2 | 2 | | | | |
| adenocarcinoma | 5 | 1 | 1 | 3 | | |
| adenocarcinoma of accessory lacrimal gland | 1 | | 1 | | | |
| lymphosarcoma | 1 | | | | 1* | |
| Fibromyxosarcoma | 1 | | | | 1 | |
| Fibrosarcoma | 1 | | | | 1 | |
| Undifferentiated sarcoma | 2 | | | 1 | 1 | |
| Sebaceous gland carcinoma | 1 | | 1 | | | |
| Granulomatous inflammation | 1 | | | ? | | |

* One in this group now deceased.

tients had no recurrence (Table 1), while the two with recurrence survived seven years and nine years, ten months, before succumbing to their disease. Simons and associates[2] experienced similar good results with basal cell carcinoma. Naquin,[1] however, encountered six tumor deaths and one additional recurrence in 10 cases of basal cell carcinoma. It is obviously important that all involved tissue and bone be excised, including sinuses, if necessary.

Our results with cases of squamous cell carcinoma have been excellent with no tumor recurrences to date. This is at variance with the experiences reported by Naquin (recurrence in the one patient followed for longer than two months) and by Simons and associates (two tumor deaths in three cases).

Melanomas, being highly metastatic, usually carry a poor prognosis. While pre-exenteration evaluation for metastases was negative in our eight patients with melanoma, an early metastasis might well have been undetectable. While metastases and tumor deaths did occur in our postexenteration melanoma patients, one year without recurrence in four of eight, five years without recurrence in three of eight, and the five-year survival of one patient with recurrence attests to the benefits of orbital exenteration in otherwise hopeless cases. Choroidal melanomas were found to have a poor prognosis even after orbital exenteration by Simons and his team (one of five patients tumor-free at three years) and by Naquin (two of eight free of disease after two years). The two patients in our series with extension of choroidal melanoma both survived five years, but one had recurrence. Conjunctival melanomas were not reported by Simons' group; Naquin reported no recurrences in three patients. Our two tumor deaths in five exenterations were not as encouraging.

Rhabdomyosarcoma has been discussed extensively by other authors with a generally accepted survival rate of approximately 50%.[3] Our small series correlates well with this figure. Even though one of our cases is alive and tumor-free after nine and one-half years without postoperative radiation therapy, we believe that radiation therapy, postoperatively, even when no tumor is known to have been left, is of value considering the severity of this particular disease process. The course of radiation therapy is usually begun two to three weeks after the operation to allow for sufficient healing. Sagerman and associates[7] reported excellent results with radiation alone after biopsy of orbital rhabdomyosarcoma. This may well prove to be adequate therapy in this disease thus excluding the use of exenteration.

Of the lacrimal gland tumors, adenocarcinoma had a poor prognosis despite apparent complete removal. Three patients with orbital lacrimal gland adenocarcinoma died of metastatic disease and one died of other causes with known recurrence within two years of operation. Follow-up for the two patients with far advanced mixed tumor was too short to allow for definite conclusions, but the results are promising to date. Naquin reported recurrences in two patients with mixed tumor of the lacrimal gland while Simons and associates did not report specific data on lacrimal gland tumors. From our experience with the misdiagnosis of adenocarcinoma on frozen sections for what was diagnosed as lymphosarcoma on permanent sections, we believe it is best to have a biopsy with permanent sections before an exenteration is done. We feel the treatment of choice in lymphomatous disease is radiation therapy or systemic chemotherapy.

The technique of orbital exenteration as outlined has worked so well with skin grafts that we believe a temporalis muscle flap should be used only in children or in patients for whom care of the socket would be difficult. The advantages of a skin-lined socket are the ability to detect recurrences early, and the ability to treat them directly. The only minor problems encountered with a skin-lined orbit have been the care of des-

quamated skin and the occasional fistula developing between the orbit and the ethmoid air cells or the nose. None of the skin grafts has reacted unfavorably to postexenteration irradiation. We have not recently used the technique of orbital granulation as this also prevents observation for tumor recurrence.

All but one of the 48 patients in this series adjusted to their postoperative appearance and care with little difficulty. The one patient had significant alcoholic and depressive problems both before and after exenteration. Many of the patients, especially those with long-standing basal cell carcinoma, stated that they felt relieved that the tumor had been removed and that the possibility of recurrence could be closely observed. Many of the patients tried prosthetic devices attached either to spectacles or directly to the skin for cosmetic improvement but all decided that a patch was better. Their main objections to the prosthesis were: a fixed-stare appearance, difference in "skin" color as the facial skin changed during the seasons and with age, and sensitivity to the adhesives used to attach the prosthesis.

Each patient in this series presented with a neoplasm which could not be treated by any surgical procedure less radical than an orbital exenteration if all tumor was to be removed with adequate margins. However, many of these cases could have been treated easily at an early stage of their disease but were either neglected by the patient or had inadequate surgery and/or follow-up observation. Other cases had rapidly growing neoplasms, with orbital exenteration being undertaken as an attempt to eradicate a rapidly fatal process. The success of an orbital exenteration depends upon obtaining tumor-free margins at the time of surgery and the performance of surgery prior to metastases. As previously noted, the presence of metastases may be impossible to detect. The modalities of radiation therapy, local chemosurgery, and systemic chemotherapy are of value in many cases where all the tumor cannot be removed surgically. Since these modalities were not always used in this series, and when used, were only employed in conjunction with exenteration, as felt to be appropriate for the individual case, no conclusions can be drawn as to the adequacy of using them alone.

## Summary

Forty-eight orbital exenterations were done in patients with a variety of advanced orbital neoplasms. The data showed good results in basal cell and squamous cell carcinomas; the procedure was of definite but shorter-lasting benefit in cases of rhabdomyosarcoma, melanoma, malignant mixed tumors of the lacrimal gland, and a variety of other orbital tumors. Results with adenocarcinoma of the lacrimal gland were discouraging. Adjunctive radiation therapy was used when appropriate.

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# ULTRASONIC DACRYOCYSTORHINOSTOMY

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A number of workers have successfully employed ultrasonic techniques in general surgery, neurosurgery and dentistry but few have explored the feasibility of treating ocular diseases with ultrasound.

Purnell, Sokollu, and Holasek[1] studied the possibility of repairing retinal detachment with high-frequency focused ultrasonic coagulation, and Karlin[2] investigated the use of low-frequency applications to produce chorioretinal lesions. Kelman[3] developed an ultrasonic technique, which he called phacoemulsification, to emulsify a cataractous lens in order to remove it by aspiration.

My associates and I[4] studied the general principles of low-frequency ultrasonic energy and investigated its potentials in ophthalmology. During the course of our studies, we developed a low-frequency ultrasonic apparatus specifically suited to the purpose (Fig. 1).

This paper describes our adaptation of standard ultrasonic equipment to the requisites of ophthalmic surgery and discusses the clinical application of ultrasonic resection of lacrimal bone in dacryocystorhinostomy.

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## ULTRASONIC APPARATUS

Conventional low-frequency ultrasonic systems consist of three parts: (1) a pulse generator, (2) a transducer to convert the pulses into mechanical vibrations, and (3) a concentrator to amplify the oscillations and transmit them to the desired point.

The most distinctive innovation in the apparatus we used (designed by Goljamina[4]) was its ferromagnetic transducer. It has two decided advantages: (1) Its efficiency is greater than that of conventional transducers (nickel), and (2) cooling is unnecessary, making the instrumental more convenient for surgical purposes.

Clinically, the frequencies used were 44-50 kc; experimentally, frequencies up to 100 kc have also been tried.

Although it is customary to designate the power output of ultrasonic devices in watts, this unit of measurement is unsatisfactory when ultrasonic energy is used for surgery because it makes it difficult to estimate the amount of energy required to produce the desired therapeutic effect on the tissues be-

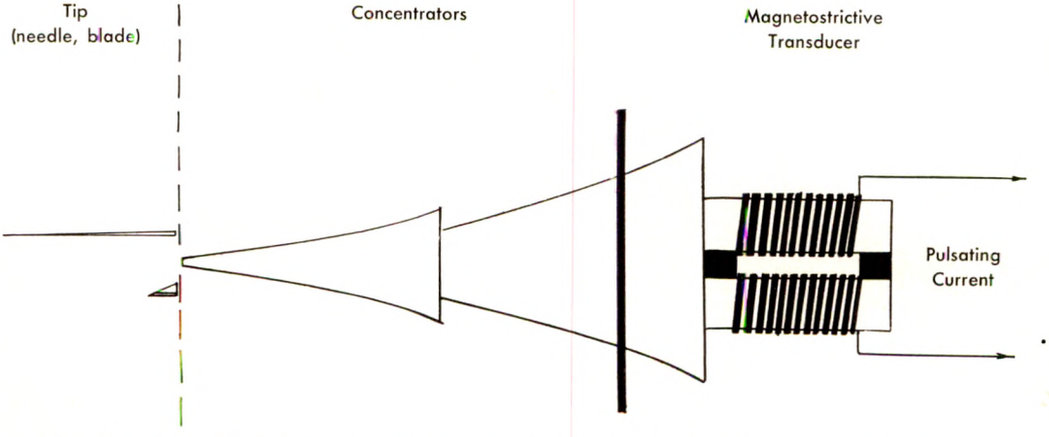



Fig. 1 (Krasnov). Block diagram of the low-frequency ultrasonic apparatus for ophthalmic surgery.

ing treated. It seemed preferable, although not ideal, to determine power output by measuring the oscillations at the concentrator tip. Oscillations up to 30 μ were used. The effect desired from the procedure dictated the type of concentrator tip: a blade for cutting, a needle for puncturing, a blunt tip for coagulating.

To correct distortions of the resonance equilibrium, which are caused by contact of the instrument tip with the tissue, an automatic frequency adjustor was incorporated in the apparatus. Installation of an "electric eye" made possible visual checking of the manual tuning. An on-off switch, conveniently operated by the surgeon, controlled the current that actuated the system.

Although the experiments conducted with this instrument included observations on the effect of low-frequency ultrasound in glaucoma, cataract removal (phacoemulsification), retinal detachment, and lamination of the cornea, only the technique for and the results of ultrasonic resection of lacrimal bone in dacryocystorhinostomy are reported here.

It is well known that the greater the acoustic resistance, the greater the loss of ultrasonic energy and, consequently, the greater its destructive power. Cutting the bone in a dacryocystorhinostomy demonstrated this clearly. Since the underlying mucosa offered less resistance to the passage of ultrasound, the effect of the ultrasonic energy on this tissue was reduced.

## Surgical technique

The first steps in the operation are conventional. After exposure of the lacrimal bone, the surgeon presses the tip of the ultrasonic instrument (a somewhat dull, spade-shaped blade is most useful) against the bone and switches on the current. The blade easily penetrates the bone in one or two seconds.

Starting from this first penetration, the surgeon continues cutting transversely with the side of the blade until he can remove a piece of bone of the desired size and shape (Fig. 2). The considerable heating that usually accompanies the cutting frequently chars the rim of the bone window, an incidental benefit for it helps to control bleeding. The mucosa may show some spots of coagulation but seldom is it perforated.

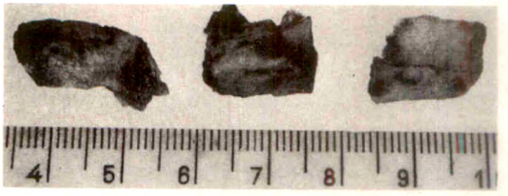



Fig. 2 (Krasnov). Bone fragments obtained by ultrasonic resection of lacrimal bone in dacryocystorhinostomy.

The usual routine completes the operation.

## Results

Follow-up periods of from two months to two and one-half years show that all but one of the 41 ultrasonic dacryocystorhinostomies performed to date were successful. These results indicate that ultrasonic resection of lacrimal bone in dacryocystorhinostomy is a simple, efficient and safe technique.

## Summary

Equipment specifically designed for exploration of the ophthalmic potentials of low-frequency ultrasonic surgery was used to investigate the effects of this modality in several eye diseases. Initial studies in 41 cases indicate that ultrasonic resection of the lacrimal bone in dacryocystorhinostomy is not only feasible but also efficient, simple, safe, and successful.

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# MEDIAN CLEFT FACE SYNDROME

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Ocular hypertelorism may occur as an isolated anomaly or in association with various congenital malformations of the facial structures, cranium, and brain. Syndromes well known to the ophthalmologist in which the eyes are widely spaced include hypertelorism of Greig, the Waardenburg syndrome, and Crouzon's disease. This paper describes the median cleft face syndrome in which the most prominent eye finding is hypertelorism.

## CASE REPORTS

*Case* 1—An infant girl was examined at the Ophthalmology Clinic of Children's Hospital at the age of nine months. The most striking finding was the grossly abnormal facial structure (Fig. 1). Pertinent external ocular findings included hypertelorism, epicanthal folds, telecanthus, and blepharophimosis. The horizontal palpebral apertures measured 12, right, and 15 mm, left. Prominent limbal epibulbar dermoid tumors were present (Fig. 2). The remainder of the ocular examination was within normal limits.

General physical examination showed a protuberance in the frontal area of the skull diagnosed as an encephalocele. The nares were extremely small and widely separated; there was a vestige of nasal tissue at each opening. Micrognathia, high-arched palate and a notched upper lip were present. The infant has shortening of the right tibia, right varus deformity of the foot, dislocation of the right hip, and polydactyly involving the lower extremities only (Fig. 3).

Psychological examination and IQ (Cattell infant scale) were below normal for age. A chromosome study showed normal female karyotype.

Pregnancy, delivery, and birth weight were normal. Family history revealed no ocular defects nor any similar developmental defects. Drugs taken during the first trimester of pregnancy were hyosamine-atropine-phenobarbital (Donnatal), meclizine HCl (Bonine), and vitamins.

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*Case* 2—This 13-year-old Caucasian girl had multiple facial anomalies: hypertelorism, a broad nasal bridge, a midline depression near the tip of the nose and a low, V-shaped frontal hair line. The eyes were structurally normal although a refractive amblyopia was present in the left eye.

Other abnormalities included craniosynostosis involving the coronal suture, left-sided cleft lip and palate and possible mental retardation.

*Case* 3—This two and one-half-year-old Caucasian girl demonstrated mild hypertelorism, mild broadening of the nasal bridge, and a small midline depression near the tip of the nose. The only ocular abnormality apart from hypertelorism was a variable horizontal strabismus ranging from esotropia to exotropia. The child's intelligence was normal. No other significant physical abnormalities were detected.

## DISCUSSION

The term "ocular hypertelorism" was used by Greig in 1924.[1] His definition excluded cases in which there were midline facial defects.

The median cleft face syndrome was first described by DeMyer.[2,3] According to his criteria, this diagnosis is made by identifying

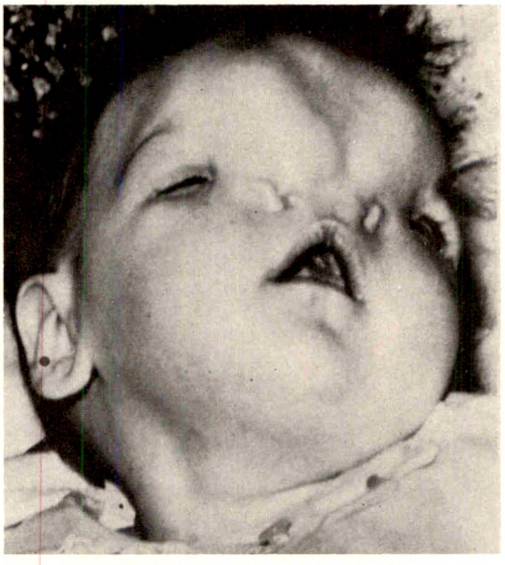


Fig. 1 (Edwards, Askew, and Weisskopf) Case 1. Nine-month-old girl with severe midline facial deformities.

two or more of the following anomalies in a patient: (1) ocular hypertelorism, (2) cranium bifidum occultum, (3) median cleft nose, (4) median cleft lip, (5) median cleft premaxilla. Other features which may be present are: (6) a low, V-shaped frontal hair line, (7) median cleft palate, and (8) primary telecanthus. Median lipomas, median teratomas, and frontal encephaloceles have been found rarely with a median cleft face syndrome. The eight anomalies listed above may occur alone or in combination in an otherwise healthy individual. They may also occur in patients with other extrafacial defects. This last group of patients may represent other diagnostic categories.

In addition to that of DeMyer, other reports have recently described cases with features of the median cleft face syndrome.[4,5] One author had previously used the term "frontonasal dysplasia" to designate this syndrome.[5]

The following ocular abnormalities have been described in patients with the median cleft face syndrome: hypertelorism, telecanthus, epicanthal folds, epibulbar dermoid tumors, exotropia, and microphthalmos (unilateral).

DeMyer has subdivided the median cleft face syndrome into four major facial patterns ranging from Facies I: all the major defects being present to a marked extent, to Facies IV: median cleft nose and hypertelorism only (the defects may be mild). Our three cases demonstrate a broad range of deformity falling within the syndrome.

Case 3 had two of the features of the median cleft face syndrome—mild hypertelorism and a small, midline depression near the tip of the nose.

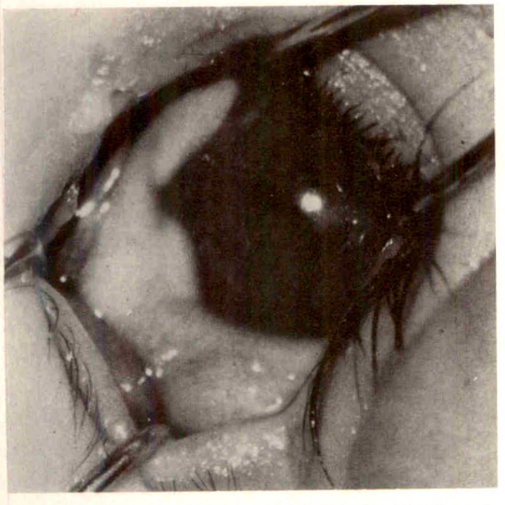


Fig. 2 (Edwards, Askew, and Weisskopf) Case 1. Left eye showing two limbal dermoid tumors.



Fig. 3 (Edwards, Askew, and Weisskopf) Case 1. Shortened right lower extremity, varus deformity of the right foot and polydactyly involving both lower extremities.

Case 2 is more severely affected demonstrating greater hypertelorism, a pronounced midline depression of the nose, and a low, V-shaped frontal hair line. In addition, the patient had craniosynostosis involving the coronal suture resulting in foreshortening of the head and a left-sided cleft lip and palate. These latter anomalies may remove this patient from the category of the median cleft face syndrome.

Case 1 illustrates severe hypertelorism and median cleft nose. She also had a notched upper lip and possibly a frontal encephalocele. This patient's facial features are compatible with those of the median cleft face syndrome and she closely resembles a published photograph of a child with this diagnosis.[5] Other congenital anomalies involving the lower extremities are also present in our patient. Extrafacial anomalies have been reported in patients with this syndrome, such as clinodactyly and partial thumb duplication.[2]

The finding of hypertelorism may be difficult to diagnose. Anomalies of other facial structures may make the eyes appear widely spaced where the actual intraocular and interorbital distances are not large. Posteroanterior skull radiographs may provide determination of intraorbital hypertelorism in patients with a craniofacial defect. Standards of normal interorbital distances determined roentgenographically for different age groups have been published.[6,7]

Ocular hypertelorism occurring alone in high degree or with certain other extrafacial anomalies carries a high probability of mental retardation[2]; however, if ocular hypertelorism is combined with one or more of the medial facial anomalies forming a pattern of the median facial cleft face syndrome, the probability is that the intelligence will be normal or near normal.[2] This is true even in the presence of severe facial malformation. Such a favorable likelihood of near normal or normal intelligence may not apply to patients with certain extrafacial anomalies in addition to features of the median cleft face syndrome.[2]

Abnormalities of the median facial structures may occur in association with hypotelorism. In these cases the probability of anomalous development of the brain and consequent psychomotor impairment can be correlated with the severity of the facial deformity. Only the patient with a mild degree of facial malformation may be expected to have a normal intelligence and potential for development. More severely affected individuals do not usually survive the first few years of life.[8]

In the view of one author[4] the median cleft face syndrome is not hereditary; however, DeMyer[2] has stated that familial occurrence of the full syndrome is quite rare, although individual features of the syndrome are more commonly familial. Although full-blown cases do not seem to be genetically transmitted, future investigation may reveal forme fruste defects in family members of individuals affected by the full syndrome.

In regard to etiology, possible relationship of drugs to birth defects may also be considered. In certain animals excessive administration of meclizine has shown teratogenic effects and has caused cleft palate, microstomia, and micromelia (short limbs).[9,10]

## Summary

Three cases are presented which demonstrate variations of a developmental disorder known as the median cleft face syndrome. The diagnosis of this syndrome is made by identifying two or more of the following anomalies in a patient: (1) ocular hypertelorism, (2) cranium bidfidum occultum, (3) median cleft nose, (4) median cleft lip, (5) median cleft premaxilla. The most consistent and prominent ocular finding associated with this syndrome is hypertelorism. Other ocular abnormalities include telecanthus, epicanthal folds, epibulbar dermoid tumors, exotropia, and microphthalmos. Some patients demonstrate mild anomalies of the mid-face region

whereas others have very marked deformities.

ACKNOWLEDGMENT

We thank Mr. Thomas Van Cader for these photographs.

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### OPHTHALMIC MINIATURE

The Duke of York (afterwards James II) expressed a great desire to see old Milton of whom he had heard so much. The King felt no objection . . . and afterwards, James went privately to Milton's house, where . . . a free conversation ensued between those very dissimilar and discordant characters. The Duke asked Milton whether he did not regard the loss of his eyesight as a judgment inflicted on him for what he had written against the late king. Milton's reply was: "If Your Highness thinks that the calamities which befall us here are indications of the wrath of Heaven, in what manner are we able to account for the death of the King, your father? The displeasure of Heaven must, upon this supposition, have been much greater against him than against me: for I have lost only my eyes but he lost his head." Much discouraged by this answer the Duke took his leave.

Symmons
Life of Milton

# NOTES, CASES, INSTRUMENTS

## PSEUDO-EXFOLIATION OF THE LENS AMONG THE NAVAJO INDIANS

H. WADE FAULKNER, M.D.
*Phoenix, Arizona*

The reported incidence of pseudo-exfoliation of the lens in people over the age of 60 years has varied from 2% in Switzerland[1] to 17% in Norway.[2] Recently Aasved[3] reviewed the geographical distribution of pseudo-exfoliation and reported its incidence in Norway, England and Germany to vary from 2.7 to 7.7% in people over 60 years of age.

This paper reports the high incidence of pseudo-exfoliation of the lens among the Navajo Indians living on their reservation in this country.

### MATERIAL AND METHOD

Fifty consecutive new patients, 60 years of age and older, attending the eye clinic at the United States Public Health Service Indian Hospital in Tuba City, Arizona, were evaluated for pseudo-exfoliation. The evaluation included best corrected visual acuity, slit lamp examination, applanation tonometry, gonioscopy, and ophthalmoscopy after dilatation of the pupil with 10% phenylephrine HCl. The diagnosis of pseudo-exfoliation was made by observing the typical dandruff-like deposits on the anterior lens capsule, pupillary margin, and trabecular meshwork.

Three patients with pseudo-exfoliation (two were normotensive and one had glaucoma with field loss in one eye only) were hospitalized and topical dexamethasone, 0.1%, was administered to one eye four times daily for six weeks. They were followed with weekly applanation pressures and tonography.

From the Department of Ophthalmology, USPHS Indian Hospital, Phoenix, Arizona.
Reprint requests to H. Wade Faulkner, M.D., 1359 Springhill Avenue, Mobile, Alabama 36604.

### RESULTS

Nineteen (38%) of the 50 patients had bilateral pseudo-exfoliation of the anterior lens capsule. Three patients (6%) had glaucoma capsulare with pathologic cupping and glaucomatous field loss.

All three patients who were tested with topical corticosteroids were "non-responders." Intraocular pressure in the tested eye never exceeded 20 mm Hg. One of the patients tested with topical corticosteroids had glaucoma capsulare in one eye and there was pseudo-exfoliation of the lenses of both eyes. The tested eye was otherwise normal in all respects, including full fields, applanation pressures of 15 and 18 mm Hg, water provocative tonography, and grade four open angles.

### DISCUSSION

Pseudo-exfoliation of the lens is a common, although previously unreported, finding in elderly Navajo Indians. Glaucoma (glaucoma capsulare) is frequently associated with pseudo-exfoliation.[4] There is debate as to whether glaucoma capsulare is secondary to the pseudo-exfoliation or a manifestation of genetically inherited primary open-angle glaucoma. Eyes with a tendency toward genetically inherited primary open-angle glaucoma respond to topically administered corticosteroids with significant intraocular pressure elevations.[5] The incidence of positive corticosteroid responsiveness is approximately the same in the Southwestern Indians as in other United States population groups.[6]

Recently, Gillies[7] reported corticosteroid responsiveness in the opposite eye in only one of six patients with bilateral pseudo-exfoliation and unilateral glaucoma capsulare. This data, combined with a similar patient

reported here, strongly suggests that glaucoma capsulare is either a secondary glaucoma or at least a glaucoma not related genetically to corticosteroid responsiveness.


## Summary

Nineteen (38%) of 50 consecutive Navajo Indians, aged 60 years or more, who attended the eye clinic of the USPHS Indian Hospital in Tuba City, Arizona, were found to have psuedo-exfoliation of the lens capsule. In three (16%) of the 19, the pseudo-exfoliation was associated with open-angle glaucoma.


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# PARADOXICAL ELEVATION OF EYELID ON SMILING


Trevor H. Kirkham F.R.C.S.

*Oxford, England*



An unusual synkinetic movement of the left upper eyelid which occurred only on smiling is reported for its rarity.


## Case report

A girl, aged 16 years, attended for a refraction appointment. Visual acuity was 6/6 in each eye. The ocular movements were full. There was a left blepharoptosis of 2 mm, but a good eyelid fold (Fig. 1) and large range of levator action was present. Bell's phenomenon was present equally on both sides. Movements of the jaws or tongue had no effect on the ptotic eyelid, but when she smiled, the ptotic eyelid elevated so that the palpebral apertures were symmetrical and it remained elevated for as long as she maintained her smile (Fig. 2). Both voluntary and involuntary smiling produced the synkinesis. No other facial movements had any effect on the position of the eyelid, and no synkinesis with other cranial nerves was demonstrable.



Fig. 1 (Kirkham). To show the left blepharoptosis.



Fig. 2 (Kirkham). The left eyelid elevates on smiling.

A photograph taken at the age of two years showed that the left blepharoptosis had remained unaltered over the years. There was no family history of any congenital abnormalities.

## Comment

The most frequent congenital synkinetic movement of the upper eyelid is the Marcus Gunn phenomenon of jaw winking; this is believed to be due to a part of the motor supply for the lateral pterygoid muscle terminating in the levator palpebrae superioris, which thus has a dual innervation. Rare synkinetic movements of the upper eyelid in association with contraction of other extraocular muscles are summarized by Duke-El-


Reprint requests to Trevor H. Kirkham, F.R.C.S., Eye Department, the London Hospital, Whitechapel, London E. 1, England.

der.[1] An interesting boy who had the Marcus Gunn phenomenon but who also had synkinetic eyelid retraction on sternomastoid contraction and on tongue protrusion was described by Parry[2]; no synkinesis occurred with facial movements. However, synkinetic eyelid retraction on smiling, but not on voluntary facial movements, as well as on activation of the ipsilateral sternomastoid and on coughing and performing the Valsalva maneuver, was described by Bradley and Toone.[3] Smiling, but not voluntary movement, produced the synkinesis which led them to believe that supranuclear connections between the nerves were involved and that a congenital abnormality of neuronal connections in the brain stem was the most likely explanation of the widespread synkinesis present in their case. The present case demonstrates that, whatever the anatomical site of the lesion, the final common pathway for voluntary and involuntary smiling is the same.

## Summary

A girl who showed congenital synkinetic retraction of the left upper eyelid on both voluntary and involuntary smiling is described.

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## Ophthalmic miniature

"And you processed her?"

"I processed her. But giving drugs to a cat is no joke, Kemp! And the process failed."

"Failed?"

"In two particulars. These were the claws and the pigment stuff—what is it? At the back of the eye in the cat. You know?"

"Tapetum."

"Yes, the tapetum. It didn't go. After I'd given the stuff to bleach the blood and done certain other things to her, I gave the beast opium, and put her, and the pillow she was sleeping on, on the apparatus. And after all the rest had faded and vanished, there remained the two little ghosts of her eyes."

H. G. Wells
The Invisible Man

# MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

## 91ST CONGRESS OF THE OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

The meeting of the 91st Congress was held in the Royal College of Physicians, London, under the presidency of Prof. George Scott of Edinburgh April, 21-25, 1971. It was attended by 400 members together with guest speakers from all parts of the world.

The Bowman lecture, in honor of Sir William Bowman, the first President of the O.S.U.K., was delivered by Dr. Algernon B. Reese of New York. His highly informative lecture was entitled, "Expanding lesions of the orbit," a subject of increasing interest in the past few years, and one in which the speaker is a recognized authority with broad experience for many years. His very well-organized material was based on a meticulous study and survey of more than 500 cases. It put us far along the road of understanding the nature and the surgical treatment of these lesions. Dr. Reese's Bowman Lecture, in the words of a British colleague was "jolly good!" The extra high quality that a Bowman Lecture demands was fully achieved. Dr. Reese now joins with the immortal names of the other four Americans who have been honored by the Society's greatest honor. These are DeSchweinitz, Arnold Knapp, J. H. Dunnington, and Michael Hogan.

The first symposium was on the dry eye, the opening speakers being Prof. Claes Dohlman, Mr. Peter Wright, Dr. J. M. Gumpel, and Dr. Ian A. Mackie. Dohlman described his recent work on the role of the mucus derived from the conjunctival goblet cells, for the stability of the tear film. He thought that there were probably two basic types of the dry eye syndromes—a primary aqueous tear deficiency, such as occurs in keratoconjunctivitis sicca in rheumatoid arthritis, and a mucus deficiency in a condition such as the Steven-Johnson syndrome, early pemphigoid, and avitaminosis A.

Mr. Peter Wright discussed the management of the dry-eyed patient and the efforts being made to find the ideal tear solution. It would appear that gel contact lenses do not seem to be the answer. It seems doubtful if gel lenses will fulfill the promise excited on their introduction as a new therapeutic weapon.

The second symposium took the form of a discussion of the ischemic eye and the 16 papers on this subject, contributed by speakers from all over the world, constituted the most comprehensive review that has ever been held at one meeting of any society. Prof. W. R. Keatinge discussed the mechanism of vessel closure and stressed that the vessel wall tension is not greatly affected by distension. A critical internal closing pressure exists, below which the vessel closes completely. The large arteries can sometimes contract with enough force to shut the lumen completely in the presence of a normal arterial pressure. He pointed out that smooth muscle contraction is produced mainly by adrenergic nerve fibers. However, it may also be excited by direct irritation of smooth muscle cells. Recent work has shown that the adrenergic nerve fibers are distributed only to the outer part of the walls of the arteries and that they probably produce their effects in part by producing action potentials in the smooth muscle cells.

Dr. David Knox discussed the various etiologic factors in ischemic ocular disease and Dr. H. Bettelheim described the use of ophthalmodynamography in the investigation of acute and chronic ocular ischemia.

Dr. Clifford Rose and associates discussed the radiologic investigation and surgical treatment of sudden blindness due to extracranial vascular lesions and described their

findings in 28 patients with monocular blindness investigated by archangiography. Sixty-eight percent of these patients had lesions affecting the carotid and 48% had verified vertebral lesions: two patients exhibited the sublavian steal syndrome, which is amenable to surgery. Only 28% of such patients appeared to have lesions sufficiently severe to require surgery. The indications for surgery were clearly outlined.

Dr. S. S. Hayreh gave a most interesting account of his recent research on posterior ciliary artery occlusion and emphasized that the two (or three) large posterior ciliary arteries arising from the ophthalmic artery divide into multiple branches near the globe and supply the blood to the choroid, optic disk and the retrolaminar part of the disk in a segmental fashion.

Dr. Paul Henkind in reviewing ischemia of the posterior segment of the eye, stressed that the knowledge of the angio-architecture of the retina, choroid, and optic nerve head must be considered in conjunction with the microcirculatory dynamics of these regions if we are to understand the various patterns of ischemia that can occur. He discussed the role of ischemia in a number of conditions such as branch and central artery occlusions, diabetes, hypertension, giant-cell arteritis, and malignant atrophic papulosus (Degos' disease).

The many other papers read included a review of the clinical and electron microscopic aspects of corneal dystrophy by Dr. Michael Hogan, and the scanning electron microscopy of the cornea, by Drs. Haining and McLean. Mr. J. Penman gave a fascinating account of facial pain and its treatment, and Mr. Hung Cheng and co-workers described the use of fluorescein angiography in the study of the iris vessels.

Mr. Dermot Pierse showed an excellent film, illustrating some new points in the technique of iridocyclectomy.

The Congress was a great occasion, with the meetings of the International Council of Ophthalmology, of the Verhoeff Society (celebrating its 25th anniversary), and of the European Ophthalmic Pathology Society all there to stimulate lively disagreement, sometimes acrimonious! The annual banquet of the society was held on Thursday evening, April 22, in the Park Lane Hotel. It was formal, sparkling, and gracious traditional affair. After the toast to Her Majesty, the Queen, Sir John Richardson, President of the Royal Society of Medicine, proposed a witty toast to the health of the D.S.U.K. This was responded to by President Scott in most gracious terms. The customary "toast to the guests" was proposed by Prof. Norman Ashton, still in a state of blissful shock on learning of his election as Fellow of the Royal Society but a few weeks before. This back-bowing burden, however, did not prevent him from exceeding his reputation as the "Bob Hope" of Ophthalmology. Prof. Jules François, President of the International Council of Ophthalmology, then replied for the guests in impeccable English and with good humor. It was a very nice party.

The smashing success of this annual meeting of a great and ancient organization lies in the attraction of the largest-ever attendance by its own membership. The large lecture hall of the Royal College of Physicians was filled to capacity every day from nine o'clock in the morning until five in the afternoon.

The next annual Congress of the O.S.U.K. will be held in Edinburgh, the home of President Scott, April, 11 through 13, 1972. It promises to be a caledonian charivari. Inquiries regarding this meeting should be addressed to the Secretary, The Ophthalmological Society of the United Kingdom, Royal College of Surgeons, Lincoln's Inn Fields, London W.C., England.

George Scott, F.R.C.S.
*Edinburgh, Scotland*
Derrick T. Vail, M.D.
*Chicago, Illinois*

## ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY SPRING MEETING

The Association for Research in Vision and Ophthalmology (formerly the Association for Research in Ophthalmology) held its annual spring meeting in Sarasota April 26–30, 1971. Over 800 registrants were recorded and the program listed close to 380 papers.

It is interesting to compare these data with those of the 1969 Spring meeting, at which time it was noted that "a record number of 469 scientists attended the annual meeting of the Association for Research in Ophthalmology . . . to hear an unprecedented number of nearly 200 papers."

The papers covered a wide spectrum of topics, including clinical research, physiology and pharmacology, anatomy and pathology, visual electrophysiology, immunology and microbiology, visual psychophysics and physiological optics, and biochemistry.

Those in ophthalmology who were fearful that expanding the organization to include a large number of basic scientists would mean a de-emphasis of clinical research can "take heart" from this meeting. The clinical research program was indeed far larger this year than ever before and covered enough of a variety of subjects to please most clinicians. Indeed, there were topics of obvious clinical interest scattered throughout the basic science seminars, and one section, Immunology and Microbiology, devoted almost an entire session to topics of clinical interest.

A major topic emphasized in several of the clinical research programs was ophthalmic genetics. All types of ocular hereditary diseases were discussed. Several new conditions were described and histochemical and electron microscopic findings were detailed in numerous well-known genetic abnormalities.

One of the clinical research sessions featured topics dealing with diabetic retinopathy. In a session on the retina, numerous papers on the technology of newer laser instruments used in the treatment of retinal conditions were presented. In this same meeting, there were several interesting papers dealing with new methods for the removal of non-magnetic foreign bodies from the vitreous.

In the sessions in Physiology and Pharmacology, the four areas emphasized were circulation and intraocular pressure, recent advances in drug dynamics and drug delivery systems, neurotransmitters and transport, and permeability.

A symposium on extragenticulate visual pathways was featured in a combined meeting of the Sections of Anatomy and Electrophysiology.

Honorary membership was given to Lorand V. Johnson, long-time secretary of the Association for Research in Ophthalmology. A "Past President Plaque" was given to Jin H. Kinoshita. The Proctor Medal was given to William A. A. Rushton, who presented "Color Vision: An Approach through the Cone Pigment" as the Proctor lecture. The Friedenwald lecture was given by Claes H. Dohlman, who spoke of the "Function of Corneal Epithelium in Health and Disease." Lorin Riggs was elected a trustee.

The next meeting will again take place in Sarasota, Florida, during the last week in April. The group owes thanks to the Florida members who arranged for the facilities and to the various section chairmen who organized the excellent programs.

Alex E. Krill

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## HERPES SIMPLEX CORNEAE—ITS CENTENNIAL OF RECOGNITION

Johann Friedrich Horner (the Horner of Horner's syndrome) was the first to recognize herpetic keratitis (Klin. Mbl. Augenheilk. 9:321, 1871). He described a unilateral affection in which the painful eye exhibited a crop of minute, clear vesicles on the corneal epithelium that soon ruptured leaving slightly clouded desquamated spots. The vascularization associated with phlyctenulosis was absent. Since the diseased eye at times was on the same side as herpetic vesicles on the lips or angle of the nose, Horner concluded that the affected cornea manifested the same herpetic infection as that seen on the face, lips, and genitals. The prior confusion with phlyctenules is exemplified in *A Treatise on the Diseases of the Eye* (1870) by Soelberg Wells, who, under "Phlyctenular corneitis (herpes corneae)" says, "Sometimes the phlyctenulae are very superficial and appear in the form of small, transparent vesicles or blisters, whose epithelial covering is soon shed, leaving a small excoriation, which may easily escape detection." The vesicular form of herpetic keratitis is uncommon and the more usual appearance was mis-

interpreted for many years. As late as 1905, Berry's *Manual of Practical Ophthalmology* showed a drawing labeled "Dendritic (mycotic) keratitis," with the textual description: "The cause is not known, though it is evidently a mycotic one. It is best treated by dabbing on to its surface some absolute alcohol with a camel's hair brush." However, the association of disciform keratitis with herpetic infection was noted by Ernst Fuchs in 1901 and the metaherpetic ulcer was described by Vogt in 1930.

Our knowledge of the disease was greatly expanded by the experimental revelations of Grüter. In 1912, he transmitted this human infection to the scarified cornea of rabbits, and in 1920 transferred the herpetic keratitis in an inoculated rabbit to the cornea of a blind man. In 1924, he isolated the virus from herpetic vesicles and confirmed Horner's clinical intuition that herpes of the cornea, face, and genitals were all caused by the same organism. In later studies Grüter observed in his rabbits the evolution of disciform keratitis from which he likewise recovered the herpes simplex virus. Grüter's evidence that the experimentally induced herpetic keratitis in the rabbit paralleled the naturally occurring disease in man established inoculation of the rabbit cornea as a means of definite diagnosis and as an ideal model for further studies. After the herpes virus was found to grow readily on the chorioallantoic membrane and one appropriate tissue culture cells, a suspension of pure virus of a desired strain is now obtainable. When dropped on the intact rabbit cornea, punctate epithelial lesions develop within four days. The intact basement membrane becomes softened and hence too aggressive chemical cauterization or mechanical scraping may expose the stroma to viral invasion. In both rabbit and man, the herpes simplex virus is shed in tears, saliva, and sputum between recurrences, and so the ever-present virus may precipitate an attack of herpetic keratitis whenever the tissue resistance of the cornea is temporarily lowered by any of numerous trigger mechanisms such as fever, allergy, emotional disturbance, or menstruation.

Herpes simplex is the most widespread of human viral visitations. The primary infection is usually transmitted by kissing and generally is subclinical, but occasionally causes a gingivostomatitis. The neutralizing antibodies which reach a maximum titer in two weeks confer no protection, and indeed, an attack of herpetic keratitis predisposes to recurrences. Since nine-tenths of the population past age 15 are carriers, serological testing for diagnosis is valueless. The same high titer of antibodies may be present before, during, and after herpetic keratitis. The initial attack of herpetic keratoconjunctivitis may be mistaken for epidemic keratoconjunctivitis. Besides a regional adenopathy, the cornea may show small white plaques that stain faintly with fluorescein but brightly with rose bengal. Subsequent recurrences are limited to the cornea and are potentially far more serious. The usual recurrence is the pathognomonic dendritic ulcer—occasionally, a superficial punctate keratitis. Corneal hypesthesia follows rather than precedes the attack and is evident after the first week. It is readily demonstrated by the instillation of an innocuous irritating solution such as ethylmorphine HCl (Dionin), 2%, or sulfacetamide, 30%, first instilled on the affected cornea and then on the other. The degree of hypesthesia is proportionate to the extent and duration of corneal ulceration and, when marked, increases the liability of a sequential metaherpetic ulcer that appears about three weeks after the herpetic keratitis has healed. The roundish ulcer apparently results from a trophic disturbance of the cornea; no virus is detectable by even the sensitive fluorescein antibody technique or electron microscopy.

In 1936, Gundersen made a detailed study of 221 cases of herpetic keratitis. Herpes appeared elsewhere on the face in three of eight patients, but involved only the cornea in the others. In a group treated by only

atropine and heat, one of four cases resolved, but more certain and quicker recovery followed local destruction of the virus by chemical cauterization of the ulcer and adjacent epithelium. Gundersen popularized the use of iodine. He applied Tr. iodine several times until a deep chestnut brown resulted, after which the iodine was neutralized by cocaine, 4%. Patching the affected eye proved of no value. In 1961, Sery discovered that the silver ion was a more potent inactivator of the herpes simplex virus than iodine or other chemical agents. After applying silver nitrate, 0.5%, to the affected areas for a few minutes, the eye was irrigated with sterile saline. If needed, treatment was repeated in three days. This method was not advised in stromal involvement because of the possibility of silver staining.

Topical cortisone for ocular affections was introduced in 1950 and its devastating action in herpetic keratitis was very soon evident. In cases given topical or systemic corticosteroids, serious complications were five times as frequent as in those not so treated. The inhibition of interferon promoted replication of virus, ameboid ulceration, stromal involvement, secondary infection, and corneal perforation. Other deleterious drugs are local anesthetics for home use, proteolytic enzymes and epinephrine.

A signal advance in the therapy of herpetic keratitis was inaugurated by Kaufman in 1962 with idoxuridine, a nucleotide analogue. If given early, resolution promptly occurs in two-thirds of cases. The 0.5% ointment given five times daily is preferable to the 0.1% solution instilled hourly. The iodoxuridine substitution for thymidine into the DNA of the herpes virus renders its DNA defective and incapable of replication. The action of the drug is limited to the surface epithelium where the virus is readily accessible. The healthy cells of the cornea are not appreciably affected, protected by their slow rate of multiplication and the greater permeability of virus-infected cells to iodoxuridine. If the eye responds favorable to treatment in five days, the drug should be continued for two weeks; if not, chemical cauterization is indicated.

Though the virus is present in stromal herpes, its mesodermal milieu may have a moderating effect on its dermotropic virulence. Stromal involvement is seldom evident for the first two to three weeks. The late occurrence suggests that an antibody-antigen reaction is an important factor, a view supported by the reversal of disciform edema, relief of symptoms, and reduction of scarring effected by small doses of corticosteroids. When iodoxuridine ointment is used with the corticosteroids, the safety of the latter is greatly increased. To lessen the inflammatory reaction of an associated uveitis, systemic phenylbutazone (Butazolidin) is safe and effective.

James E. Lebensohn

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## OBITUARIES

### EVERETT LOGAN GOAR
### 1886–1971

Everett L. Goar, M.D., was born in Clinton County, Indiana, on November 13, 1886. He died at the age of 84 on April 25, 1971, in Houston, Texas, where he had practiced from 1921 until his retirement, January 1, 1971. He graduated from Kirklin, Indiana, high school in 1903 and from Indiana University, Bloomington, in 1907. After graduation from Rush Medical College, Chicago, Illinois, in 1909, he served his internship at Chicago's Cook County Hospital from 1909-11. During World War I, Dr. Goar became a Major in the Medical Corps. He studied ophthalmology at the New York Eye and Ear Infirmary in 1920 and at the University of Colorado in 1922, and was awarded Doctor of Ophthalmology degree from Colorado University in 1925.

Dr. Goar gave generously of his time and efforts to each of the many organizations to which he belonged. He served as president of the Harris County Medical Society, of the

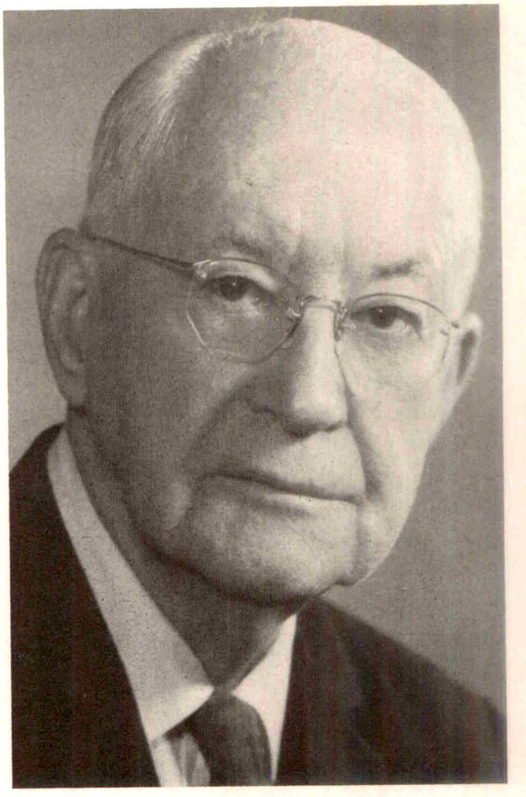
Houston Academy of Medicine, and of the Texas Society of Ophthalmology and Otolaryngology, and of the American Ophthalmological Society, 1954-55. He served as Vice President of the American Academy of Ophthalmology and Otolaryngology. He was Chairman of Section on Ophthalmology of the American Medical Association. He was a member of American Board of Ophthalmology for nine years and Chairman of the Board, 1947-48. He was Director of the National Society for Prevention of Blindness, 1952-1960, and Chiarman of the Professional Committee of the Texas Society for Prevention of Blindness. For his role in organizing the Texas Society, he received the Dana Gold Medal award in 1962.

Dr. Goar was one of the men instrumental in the moving of Baylor University College of Medicine from Dallas to Houston, Texas, in 1943. He was Professor of Ophthalmology and Head of the Department from 1943 to 1957 and was Professor Emeritus at the time of his death.

He was primarily interested in teaching the young. For his work with the Boy Scouts, he received the Silver Beaver Scouting award in 1936. Professionally as a teacher, for many years he helped give courses at the Academy on slit-lamp examinations and wrote many articles on various subjects in this field, including his "Handbook of Ophthalmology" for medical students.

He was an active church member and lived by the Golden Rule and Ten Commandments. On February 22, 1971, when he was given the Good Citizen Award by the Paul Carrington Chapter of the Sons of the American Revolution, one of the speakers stated: "This evening we gather to say thank you publicly to a sincere and unassuming man who is universally acclaimed as one of the great ophthalmologists of the world."

Shortly after his retirement, he gave his office equipment to the remote province of Kasai, deep in the African Congo, where it will continue to be of service to people who cannot afford modern equipment.



Everett Logan Goar, M.D.

A devoted family man, he is survived by his wife, Eleise Hailey Goar, and three children, E. Logan Goar, Jr., Robert Jefferson Goar, and Mrs. Fred (Ann) Babb. With the passing of Dr. Goar, ophthalmology, mankind, and his associates have suffered a great loss. His contributions to ophthalmology will long be remembered.

Jacob F. Schultz

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## ARCHIMEDE BUSACCA

Professor Archimede Busacca of San Paulo, Brazil, died March 25, 1971, in San Paulo. He is the author of Biomicroscopy and Histology of the Eye, in three volumes. In 1932 he described the floccule that bear his name which occur on the mesodermal surface of the iris in uveitis. His corneas were used for transplants immediately after his death.

## CORRESPONDENCE

### JAW-WINKING BLEPHAROPTOSIS

Editor,
American Journal of Ophthalmology:

The direct quotation ascribed to Raynold N. Berke in my paper discussing causes, types, and factors concerning congenital blepharoptosis (Am. J. Ophth. 71:696, 1971) should read: "After 20 years of trial and error I can honestly say that the surgical treatment of jaw-winking ptosis is no simple problem.

This is so because we must eliminate the jaw-winking phenomenon as well as correct the ptosis. This dual purpose can be accomplished only by excising a large part of the levator to release the bizarre behavior of the lid and then suspending the lid from the superior rectus or from the frontalis muscle.

If this principle is ignored and a resection of the levator done for the ptosis, then (at least in this author's experience) the ptosis will persist and the jaw-winking will be exaggerated.

If a large section of the levator is excised and the lid suspended from the superior rectus, an excellent result can be obtained only if the superior rectus is normal. But if this muscle is paretic, a progressive hypotropia will develop with the years; and since about two-thirds of all jaw-winkers have a weak superior rectus, some other procedure must be used for most such cases."

Edmund B. Spaeth

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## BOOK REVIEWS

CHLAMYDIA AND CHLAMYDIA-INDUCED DISEASES. By Johannez Storz, DVM. Clothbound, 358 pages, table of contents, appendix, bibliography, index, 94 black and white figures. $20

This long-awaited volume on the chlamydia will be welcomed by ophthalmologists, microbiologists, veterinarians, urologists, gynecologists, and public health workers. Prof. Storz has been successful in bringing together in one volume much important information previously available only to the worker willing and able to review a variety of journals in many different disciplines. Prof. Storz has described the fascinating biology of the chlamydial agents as well as the nature and characteristics of the many chlamydia-induced diseases. These extraordinary organisms were long thought to be viruses but are now known to be small, bacteria-like intracellular parasites lying intermediately between the rickettsiae and the larger viruses. Their wide range of hosts encompasses birds, animals, and man. Both the reaction of vertebrates to the chlamydia and the pathogenic mechanisms by which the chlamydial agents induce such types of disease as pneumonia, enteritis, polyarthritis, abortion, and keratoconjunctivitis are well described. The problems relating to immunity and the many unsuccessful vaccination trials that have been made are all fully covered.

The ophthalmologist will find much of interest in this volume since several ocular diseases in addition to trachoma are now known to be of chlamydial origin. At least five chlamydial agents—those responsible for trachoma, inclusion conjunctivitis, lymphogranuloma venereum, parakeet psittacosis, and feline pneumonitis—are now known to attack the external human eye. Uveitis is now known to occur in lymphogranuloma venereum and in rare cases of inclusion conjunctivitis. It seems likely that some cases of Reiter's syndrome, with its conjunctivitis, keratitis, and uveitis, are of chlamydial origin; and it is certainly now well accepted that chlamydial urethritis and cervicitis are widespread in the population and responsible for the fact that inclusion conjunctivitis of the newborn is the commonest type of ophthalmia neonatorum in the United States.

Prof. Storz's volume is well illustrated and the bibliography complete.

Phillips Thygeson

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# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ARCHIVES OF OPHTHALMOLOGY

VOLUME 85 FEBRUARY, 1971 NUMBER 2

DOMINANT JUVENILE OPTIC ATROPHY. Caldwell, J. B. H., Howard, R. O. and Riggs, L. A. (Yale University School of Medicine, 333 Cedar St., New Haven, Conn., Arch. Ophth. 85:133-147, Feb., 1971.

Optic atrophy, with a dominant pattern of inheritance, may occur in childhood with an insidious onset, and may be unrelated to any other neurological, congenital, or developmental anomaly. The clinical and laboratory findings are described in two families with this condition. (8 figures, 4 tables, 35 references)—Authors' abstract

TOPICALLY APPLIED CORTICOSTEROIDS IN GLAUCOMA CAPSULARE. Pohjola, S. and Horsmanheimo, A. (Helsinki University School of Medicine, Helsinki), Arch. Ophth. 85:150-153, Feb., 1971.

Eleven (28%) of 39 patients with glaucoma capsulare responded to topical dexamethasone treatment with pressure elevation of 6 mm Hg or more. It seems that glaucoma capsulare is not genetically identical with primary open-angle glaucoma and should be regarded as secondary glaucoma. Interestingly, most responders (eight out of 11) had, in addition to glaucoma capsulare in one eye, primary open-angle glaucoma in the fellow eye. (5 tables, 8 references)—Authors' abstract

PHOTOCOAGULATION THROUGH THE GOLDMANN CONTACT GLASS. Fankhauser, F., Lotmar, W. and Roulier, A. (Universitats-Augenklinik, 3000 Bern, Switzerland), Arch. Ophth. 85:154-162, Feb., 1971.

From observation of the temporal development of photocoagulation lesions generated by a quasi-continuous ruby laser source described earlier, it was concluded that lesions less densely distributed would still result in satisfactory welding of the retina. Biomicroscopic follow-up of more than 200 cases has shown that this conjecture is essentially correct. Indeed, lesions of very low pulse energy lead to strong stimulation and proliferation of pigment epithelium. Among the cases only one, that is, 0.5% developed postcoagulative maculopathy (puckering syndrome); whereas, of a comparable number treated with the Zeiss xenon photocoagulator, 3.1% were afflicted with this disease. This result is ascribed to the large difference in light energy between the xenon arc and the Siemens ruby laser apparatus required to cover comparable areas of the retina with coagulates. (3 figures, 11 references)—Authors' abstract

HYDROPHILIC CONTACT LENSES IN CORNEAL DISEASE. Leibowitz, H. M. and Rosenthal, P. (University Hospital, 750 Harrison Ave., Boston 02118), Arch. Ophth. 85: 163-166, Feb., 1971.

Patients having a superficial, sterile, indolent corneal ulcer which failed to respond to conventional therapeutic modalities were fitted with a hydrophilic contact lens. The corneal epithelium was removed prior to lens fitting, and the lens remained in place for one week. In the series of patients described, the hydrophilic contact lens proved to be an extremely useful adjunct in promoting the healing of indolent corneal ulcers. The possible mechanisms by which this effect is accomplished are discussed. (1 figure, 2 tables, 5 references)—Authors' abstract

LOWERING OF INTRAOCULAR TENSION. Mehra, K. S., Singh, R., Char, J. N. and Pajyashree, K. (Medical Enclave, Banaras Hindu University, Varanasi-5, India), Arch. Ophth. 85:167-168, Feb., 1971.

The comparative effects of isosorbide and glycerin on lowering of intraocular tension (IOT) were studied in 54 patients. With isosorbide, a greater fall occurred in 31 patients; while with glycerin, a greater fall occurred in 23. Besides lowering IOT, isosorbide produced significantly fewer side reactions than glycerin. (3 tables, 4 references)—Authors' abstract

FABRY'S DISEASE: OCULAR FINDINGS IN A FEMALE CARRIER. Weingeist, T. A. and Blodi, F. C. (Department of Ophthalmology, University Hospitals, Iowa City 52240), Arch. Ophth. 85:169-176, Feb., 1971.

It is postulated that diffuse corneal haze in Fabry's disease (angiokeratoma corporis diffusum) is due to an abnormal accumulation of sphingolipid in the corneal epithelium. The whorl-like pattern which is seen clinically in the cornea is thought to arise from the formation of a series of sub-epithelial ridges in these patients. (10 figures, 20 references)—Joel G. Sacks

$G_{MI}$—GANGLIOSIDOSIS. Emery, J. M., Green, W. R., Wyllie, R. G. and Howell, R. R. (Eye Pathology Laboratory, the Johns Hopkins Hospital, Baltimore 21205) 85: 177-187, Feb., 1971.

Infantile $G_{MI}$—gangliosidosis, a combined mucopolysaccharide-ganglioside storage disease with important ocular manifestations, is characterized by psychomotor retardation from birth, hepatosplenomegaly, skeletal changes (resembling Hurler's syndrome), peripheral pitting edema, mild corneal haze, and cherry red spots of the maculae. Pathologic studies of the eye, not previously reported, show evidence of muco-polysaccharide storage in the cornea and ganglioside storage in retinal ganglion cells. (17 figures, 31 references) —Authors' abstract

CORRECTION OF THE SUPERIOR LID SULCUS WITH SUBPERIOSTEAL IMPLANTS. Soll, D. B. (Department of Ophthalmology, University of Pennsylvania and Frankfort Hospital, Philadelphia), Arch. Ophth. 85:188-190, Feb., 1971.

A silicone implant with a self-sealing balloon on the posterior surface has been devised to fill the orbital volume from below as a means of correcting this defect. (5 figures, 5 references)—Joel G. Sacks

RECTUS MUSCLE UNION IN SIXTH NERVE PARALYSIS. Frueh, B. R. and Henderson, J. W. (Department of Ophthalmology, N309 University Medical Center, Columbia, Mo. 65201), Arch. Ophth. 85:191-196, Feb., 1971.

A rectus muscle union transferred muscle action without altering insertions on 11 eyes in nine patients with sixth nerve paralysis. Medial rectus tendon recession was also performed and is indicated for deviations greater than 25 prism diopters. The rectus muscle union tends to produce equal or superior cosmetic results and incidence of fusion, less vertical muscle imbalance, but a smaller amplitude of abduction than variations of Hummelsheim's technique. The rectus muscle union is recommended for the treatment of persistent sixth nerve palsies. (6 figures, 3 tables, 14 references)—Authors' abstract

OXYGEN STUDIES IN RETROLENTAL FIBROPLASIA. Flower, R. W. and Patz, A. (Johns Hopkins University Applied Physics Laboratory, 8621 Georgia Ave., Silver Spring, Md. 20910), Arch. Ophth. 85:197-203, Feb., 1971.

The effects of increased arterial partial oxygen tensions ($po_2$) on retinal circulation of the young kitten were investigated by observing changes in the velocity of fluorescein wave fronts in the major arterial branches of the retina. Changes in velocity were correlated with simultaneous carotid arterial $po_2$ determinations. These studies on the larger retinal vessels are the first of a series aimed at determining levels of arterial $po_2$ that can be sustained without damage to any components of the retinal vascular bed. (8 figures, 6 references)—Authors' abstract

CILIARY BODY TEMPERATURES IN CRYOSURGERY. de Roetth, Jr., A. (Institute of Ophthalmology, Columbia-Presbyterian Medical Center, New York), Arch. Ophth. 85:204-210, Feb., 1971.

Intraocular temperatures were investigated during cryosurgery of the ciliary body in albino rabbit eyes. A significant temperature differential was noted between the temperature of the cryosurgical probe and the temperature within the involved tissue. Attempts were made to relate temperature changes in the ciliary body of these rabbit eyes to the clinical course following cryosurgery for the treatment of glaucoma. The need for −80C as the optimum operating temperature is further emphasized, and the drastic changes following freezing with lower temperatures are illustrated. (2 figures, 3 tables, 8 references)—Authors' abstract

EYE CHANGES IN AUTOIMMUNE NZB AND NZB × NZW MICE. Kessler, H. S., Cubberly, M. and Manski, W. (Department of Microbiology, Room 12-515, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York), Arch. Ophth. 85:211-219, Feb., 1971.

All of the 7- to 11-month-old NZB × NZW $F_1$ mice investigated presented ocular changes which, in many respects, are analogous to those associated with Sjogren's syndrome in humans. The lacrimal and the salivary glands showed infiltrations and epimyoepithelial islands; however, lobular architecture was preserved. Superficial erosions of the conjunctival epithelium, thinning of the cornea, and formation of keratin granules in the epithelial cells without cornification were common. Lesions in the anterior chamber, lens, iris, and retina, and a decrease in lacrimation was observed. Many such changes which have not been described in Sjogren's syndrome may be associated with the immunopathological findings in these mice. Enucleation is not warranted in Sjogren's syndrome and therefore histological changes with time are not easily followed clinically in patients with this syndrome. (18 figures, 10 references)—Authors' abstract

HERPES SIMPLEX VIRUS-INDUCED CONGENITAL CATARACTS. Cibis, A. and Burde, R. M. (Washington University School of Medicine, 660 Euclid Ave., St. Louis 63110), Arch. Ophth. 85:220-223, Feb., 1971.

Herpes simplex virus (HSV) was cultured from the lens aspirate of a dense cataract present in the right eye of an 18-month-old healthy white girl. A small linear anterior cortical opacity was present in the other eye along with an unusual pattern of chorioretinal scarring. (2 figures, 24 references)—Authors' abstract

DRUSEN OF THE OPTIC DISC AND THE DEVELOPMENT OF FIELD DEFECTS. Cohen, D. N. (Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston), Arch. Ophth. 85:224-226, Feb., 1971.

Two young adults with drusen of the nerve head in association with evidence of vascular disturbance experienced the sudden onset of arcuate scotomata. (14 references)—Author's abstract

## BULLETIN DE LA SOCIÉTÉ BELGE D'OPHTALMOLOGIE

VOLUME 153 1969

COMBINED OPERATION FOR GLAUCOMA AND CATARACT. (French) François, J. (Gand), Bull. Soc. Belge Ophtal. 153:623-631, 1969.

Eighty-eight percent of 31 cases obtained a good fistula when a modified Scheie procedure was combined with cataract extraction. (5 figures, 1 table, 47 references)—Frank J. Weinstock

EARLY TREATMENT OF TRAUMATIC CATARACT. (French) Missotten, L. and Van Vlimmeren, H., Bull. Soc. Belge Ophtal. 153: 632-637, 1969.

In ocular injuries with a traumatic cataract, primary repair of a perforating wound was carried out. Ten to fifteen days later, aspiration of the cataract was done under local anesthesia. Fifteen of 23 cases resulted in 10/10 vision. Only five patients persisted in wearing a contact lens. (6 figures, 1 table, 1 reference)—Frank J. Weinstock

BIOMETRIC STUDY OF THE ANTERIOR SEGMENT OF THE EYE IN ANGLE CLOSURE GLAUCOMA. (French) Delmarcelle, Y., Luyckx, J. and Weekers, R. (Clinique ophthalmologique de l'Université de Liège), Bull. Soc. Belge Ophtal. 153:638-650, 1969.

In most cases of angle closure glaucoma, increased thickness of the lens is a major factor. Other factors are reduction of the height of the corneal dome and advancing position of the insertion of the iris on the wall of the globe. (6 figures, 1 table, 9 references)—Frank J. Weinstock

ANNULAR ELEVATION OF THE RETINA. (French) Michiels, J., Heffinck, P. and Rommel, J. (Clinique ophthalmologique de l'Universite de Louvain), Bull. Soc. Belge Ophtal. 153:651-670, 1969.

Three cases with a probable inflammatory etiology are presented. (15 figures, 23 references)—Frank J. Weinstock

INSULIN IN THE AQUEOUS HUMOR OF MAN (RADIO-IMMUNOLOGICAL DETERMINATIONS). (French) Toselli, C. (Clinique ophthalmologique Université catholique de Rome), Bull. Soc. Belge Ophtal. 153:671-674, 1969.

Diagnostic paracenteses were carried out and analyzed. The quantity of insulin in the aqueous was 12 ± 2 $\mu$ U/ml which was 38.7% the value of insulin in the plasma (31 ± 8 $\mu$ U). (11 references)—Frank J. Weinstock

CLINICAL MEASUREMENT OF THE CHOROIDAL BLOOD PRESSURE. (French) Fritz, A., Bull. Soc. Belge Ophtal. 153:702-712, 1969.

Blanching of the pink color of the optic disc with pressure on the globe is related to the choroidal blood pressure. The choroidal pressure varies due to the vasomotor activity of the choroid. Below a mean retinal artery pressure of 46 to 55 mm Hg the choroidal pressure exceeds the retinal pressure by 1.3 to 7.7 mm Hg whereas above this level the choroidal pressure is 4.8 to 14.1 mm Hg lower. (2 figures, 1 table, 16 references)—Frank J. Weinstock

## CANADIAN JOURNAL OF OPHTHALMOLOGY

VOLUME 5 JULY, 1970 NUMBER 3

CRYOFIXATION—CONTROL OF OCULAR SHAPE AND MOVEMENT BY CRYOADHESION. Shea, M. (828 Medical Arts Building, 170 St. George Street, Toronto 180, Ontario, Canada), Canad. J. Ophth. 5:207-214, July, 1970.

Prior to intraocular surgery, cryofixation ring is placed approximately 7 mm from the limbus and adheres to the sclera for its entire area of contact. This device prevents indentation of the globe by lid pressure, prevents distortion of the globe, and eliminates rotational movement about an axis vertical to the plane of the cryofixation ring, thus facilitating incision of the cornea and intravitreal manipulation. Because the cryofixor is rigidly mounted to the operating table, no patient movement can be permitted and general anesthesia is required. Two of 27 patients developed localized choroidal hemorrhages which did not affect the outcome of the surgical procedure. (4 figures, 4 references)—R. Theodore Goldberg

THE EFFECT OF AIR POLLUTANTS ON THE EYE. Waheed, M. A. and Basu, P. K. (Department of Ophthalmology, University of Toronto, 1 Spadina Crescent, Toronto 179, Ontario, Canada), Canad. J. Ophth. 5:226-230, July, 1970.

A sample of an organic extract of atmospheric pollutants was applied directly to the palpebral conjunctiva of albino rabbits. After eight days there was a small but definite decrease in the number of goblet cells. It is possible that this reduction occurred by direct injury of the goblet cells or the extract might have affected the goblet cell precursors and thus interfered with the production of fresh cells. (4 figures, 1 table, 16 references)—R. Theodore Goldberg

THE USE OF MAGNESIUM ON HERPETIC ULCERS OF THE CORNEA. (French) Côté, G., Smith, G. and Rochette, J. (Hôpital du Saint-Sacrement, 1050 Chemin Ste-Foy, Québec, P. Q., Canada), Canad. J. Ophth. 5:231-238, July, 1970.

Large doses of systemic magnesium in rabbits produced noxious effects. In contrast, in man, small doses systemically produced satisfactory effects. A topical solution of 10% magnesium sulphate gave good results in both man and rabbits. (10 figures, 7 references)—Authors' abstract

CORNEAL COMPLICATIONS OF TOPICAL ANESTHETIC ABUSE. Willis, W. E. and Laibson, P. R. (Will Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pennsylvania), Canad. J. Ophth. 5:239-243, July, 1970.

Nine patients are reported in whom topical anesthetics were used repeatedly to relieve the pain of corneal lesions. In six of these there was extension of edema and erosions because of the anesthetic. Topical anesthetics may interfere with normal corneal re-epithelialization by inhibiting corneal respiration and decreasing epithelial mitotic activity. The danger of repeated applications of topical anesthetics is emphasized. (2 figures, 1 table, 14 references)—R. Theodore Goldberg

REMOVAL OF NON-MAGNETIC INTRAOCULAR FOREIGN BODIES USING THE IMAGE INTENSIFIER. Anhalt, E. F., Oppenheim, R. S. and Konkal, J. (Winnipeg Clinic, St. Mary's Avenue and Vaughan St., Winnipeg 1, Manitoba, Canada), Canad. J. Ophth. 5:244-247, July, 1970.

The authors describe a technique for localizing and removing nonmagnetic intraocular foreign bodies in the presence of opaque media, with the aid of the image intensifier. Once the forceps are introduced into the globe, the position of both the foreign body, and the forceps can be magnified on a large viewing screen. By rotating the ampule 90° the operator can view both the forceps and the intraocular foreign body in two planes 90° apart. With alternating perpendicular and horizontal views, the forceps can be guided to the foreign body. (5 figures, 4 references)—R. Theodore Goldberg

MICROSPHEROPHAKIA. Michaud, C. (450 est, rue Sherbrooke, Ste 250, Montréal 24, P. Q. Canada), Canad. J. Ophth. 5:252-254, July, 1970.

The etiology, symptoms, signs, and treatment of this condition are reviewed. The author stresses the importance of thorough examination of all high myopes, particularly myopic children with elevated intraocular pressure, to detect this entity. (2 references)—R. Theodore Goldberg

MYCOLOGY OF EYE BANK EYES I. STUDIES ON THE FROZEN-STORED DONOR MATERIAL. (Department of Ophthalmology, University of Toronto, 1 Spadina Crescent, Toronto 179, Ontario, Canada), Canad. J. Ophth. 5:255-263, July, 1970.

Eighteen out of 32 frozen-stored donor eyes were found to be contaminated with a variety of fungi. The sterilization of donor eyes with merthiolate, pretreatment with glycerine and freezing at −65°C. and thawing, and even three subsequent saline washings of the eyes did not appear to have much effect in removing fungi from the donor eyes. Frozen-stored cornea was found to be a suitable media for the growth of both pathogenic and non-pathogenic fungi. (14 figures, 17 references)—R. Theodore Goldberg

CHLOROQUINE RETINOPATHY IN THE RABBIT. Ramsey, M. S., Bloodworth, J. M. B. and Engerman, R. L. (Department of Pathology, University of Wisconsin, 470 North Carter Street, Madison, Wisconsin 53705), Canad. J. Ophth. 5:264-273, July, 1970.

Oral administration of chloroquine to rabbits for 35 weeks produced the following light and electron microscopic findings in the retina and choroid: (1) membranous cytoplasmic bodies present in the enlarged ganglion cells and to a lesser degree in other cells of the retina, especially enlarged pigment epithelial cells, (2) mixed osmiophilic bodies present in all layers of the retina and especially in the enlarged pigment epithelial cells, and (3) migration of pigment granules from the pigment epithelium to the outer layers of the sensory retina. The authors suggest that the basic defect in chloroquine retinopathy is a drug-induced lyosomal disorder. (9 figures, 23 references)—R. Theodore Goldberg

TRANSVITREAL ELECTROCOAGULATION OF RABBIT FUNDAL VESSELS. Fejer, T. P. and Shea. (Department of Ophthalmology, Faculty of Medicine, University of Toronto, 1 Spadina Crescent, Toronto 179, Ontario, Canada), Canad. J. Ophth. 5:274-283, July, 1970.

Because of the limitations of photocoagulation in obliterating vessels which are projecting into the vitreous in retinitis proliferans, the authors investigated the transvitreal electrocoagulation of rabbit fundal vessels. They passed an insulated coagulating needle through the pars plana of the rabbit. Thirteen eyes were treated. In five the treated vessels were completely obliterated, seven showed a 75% decrease in vessel diameter, and one showed a 50% decrease in vessel diameter. (6 figures, 6 references)—R. Theodore Goldberg

EXPERIMENTAL PHLYCTENULAR KERATITIS. Davis, P. L., Watson, J. I. and Sapp, G. A. (Department of Ophthalmology, Royal Victoria Hospital, Montreal, Quebec), Canad. J. Ophth. 5:284-292, July, 1970.

The authors believe that phlyctenular keratitis occurs when cell wall antigens from lid bacteria enter the cornea at sites of corneal epithelial loss and combine with specific precipitating antibodies. To test this hypothesis, bovine serum albumen was used to immunize

rabbits. Their abraded corneas were then challenged with the immunizing antigen. The control eyes did not react, but the test dyes developed lesions which grossly and histopathologically resembled those of human phlyctenular keratitis. (12 figures, 10 references)—R. Theodore Goldberg

A METHOD FOR STUDYING THE ANTIBODY-PRODUCING CELLS FROM THE CORNEAL AND CONJUNCTIVAL TISSUES. Basu, P. K. and Carré, F. (Department of Ophthalmology, University of Toronto, 1 Spadina crescent, Toronto 179, Ontario), Canad. J. Ophth. 5:293-296, July, 1970.

Rabbits were immunized with sheep serum in Freund's complete adjuvant and two weeks later they were challenged with an intracorneal injection of the same serum. Four days later samples of the conjunctiva, cornea, and limbus were implanted in tissue culture. The migrating lymphoid cells were trypsinized after four days and tested for their plaque-forming capabilities. A special shallow glass chamber was used to facilitate observation and photography of the plaques. (3 figures, 6 references)—R. Theodore Goldberg

## JAPANESE JOURNAL OF OPHTHALMOLOGY

VOLUME 14 JULY-SEPTEMBER, 1970 NUMBER 3

A NEW CORNEA-POSITIVE POTENTIAL IMMEDIATELY FOLLOWING THE EARLY RECEPTOR POTENTIAL. Yonemura, D. and Hasui, I. (Department of Ophthalmology, School of Medicine, Kanazawa University, Takara-machi, Kanazawa, Japan), Jap. J. Ophth. 14:159-171, July-Sept., 1970.

In the albino rat this appears between the negative phase of the early receptor potential, and the a-wave. The amplitude of this newly described wave is directly proportional to the stimulus intensity, and the threshold is extremely high. (11 figures, 30 references)—Paul A. Hein, Jr.

GENETIC STUDIES ON DEFECTIVE COLOR VISION IN JUNIOR HIGH SCHOOL STUDENTS. Ichikawg, H., Majima, A., Komatsu, S. and Tokita, H. (Department of Ophthalmology, Central Hospital of Japanese National Railways, Tokyo), Jap. J. Ophth. 14:202-209, July-Sept., 1970.

Virtually the entire junior high school population of Rishiri Island was studied. Color vision defects were found in 6.83% of the males, 1.93% being protan and 4.76% deutan. Among females, 0.8% showed defects, 0.16% protan and 0.64% deutan. (4 tables, 1 reference)—Paul A. Hein, Jr.

FINE STRUCTURE OF EXTRAOCULAR MUSCLES IN MYASTHENIA GRAVIS. Sakimoto, T. (Department of Ophthalmology, School of Medicine, University of Tokyo Bunkyo-ku, Tokyo), Jap. J. Ophth. 14:210-222, July-Sept., 1970.

Small, abnormal muscle fibers were grouped within apparently normal ones. In the center of these abnormal fibers were found numerous exceptionally large mitochondria, some of which showed inclusion bodies. The findings are not unlike those of thyroid myopathy. (11 figures, 1 table, 36 references)—Paul A. Hein, Jr.

## OPHTHALMOLOGICA

VOLUME 160 1970 NUMBER 5

THE CAUSES OF BLINDNESS IN 156 VISUALLY AND MENTALLY DEFECTIVE CHILDREN. Copper, A. C. and Schappert-Kimmijser, J. (Zutphen, the Netherlands), Ophthalmologica 160:292-302, 1970.

These children were the inmates of an institution for the multiply handicapped. The mental status of most of the subjects precluded valid testing of photoreceptor function and made the ophthalmological examination incomplete. From the combined medical data the probable cause of blindness could be determined in about 70% of the cases. There remained about 22 congenital cataracts and 17 gross congenital ocular anomalies without any clue to the cause of the defect. A preliminary comparison was made between the principal causes of blindness in mentally defective and mentally normal children. In the latter hered-

ity accounted for twice as much blindness as in the former. (13 tables, 3 references)—Peter C. Kronfeld

REFLECTIONS OF LIGHT FROM THE OCULAR FUNDUS. Planten, J. T. (Leeuwarden, the Netherlands), Ophthalmologica 160:303-305, 1970.

The paper deals with the well-known irregular reflections from the area around the disc and around the macula which are seen through the direct ophthalmoscope and the dilated pupil and are normally most pronounced in youngsters between 8 and 14 years of age. Examination with the fundus contact glass indicates that these reflections are located between retina and vitreous. According to the essayist's observations the pattern of these reflections becomes more marked in pathological conditions associated with slight elevations of the intracranial pressure. Inflammation of the optic nerve can also be accompanied by an increase in the number of reflecting ridges and folds. The author offers the theory that under the conditions of raised intracranial pressure fluid from the perivascular spaces in the optic nerve seeps into the boundary between retina and choroid (cfr. Gärtner, Ophthalmologica 153: 367, 1967)—Peter C. Kronfeld

INJECTION OF RADIOACTIVE $S^{35}$: A NEW TREATMENT FOR IRIS AND CONJUNCTIVAL CYSTS. Mesker, R. P., Oosterhuis, J. A. and van der Schoot, J. B. (Department of Ophthalmology and Radiology, University of Amsterdam), Ophthalmologica 160:308-313, 1970.

$S^{35}$, an emitter of soft beta-rays, was used for the authors in two cases, one large congenital anterior chamber cyst and one large posttraumatic subconjunctival cyst. Injected as the highly soluble sodium sulfate, the isotope was ineffective; as insoluble, finely suspended barium sulfate it produced regression of the cysts. Both injections were well tolerated, without any adverse effects on lens epithelium or corneal endothelium coming to the fore. The authors add that it may be wise to remove the contents of the cyst by aspiration some time after injection of the radioactive barium sulfate in order to promote more shrinkage of the cyst. (6 figures, 13 references)—Peter C. Kronfeld

MALIGNANT MELANOMA OF THE CHOROID: AN UNUSUAL VARIANT. Donders, P. C. (Groningen, the Netherlands), Ophthalmologica 160:314-318, 1970.

The medium-sized choroidal tumor (from an 58-year-old, otherwise well female) appeared, at first glance, to be of vascular origin. It was composed of fairly loose tissue containing a large number of vessels of various sizes and of vacuoles some of which were filled with blood cells. Around the blood vessels the tumor tissue was more compact and made up of large irregularly shaped cells with polymorphous nuclei. Some of the cells contained melanin. The tumor had invaded the sclera and was, therefore, probably malignant. After considering various vascular tumors the author feels that the diagnosis, from the presence of melanin and the invasive tendency, must be malignant melanoma. (4 figures, 6 references)—Peter C. Kronfeld

READING DISORDERS. Velzeboer, C. M. J., de Wit, J. and Hagedoorn, J. M. (University Eye Clinic, Vrije Universiteit, de Boelelaan, Amsterdam), Ophthalmologica 160:319-320, 1970.

There is unanimity in the Netherlands regarding the role of the peripheral visual organ in developmental dyslexia. A systematic search for organic or perceptual ocular anomalies in the pupils of the Pedologic Institute in Amsterdam has failed to show any relationship between ocular anomalies and dyslexia. "The best way to handle a child with dyslexia must be found by cooperation between doctor, psychologist and teacher. The pedagogue, with great ingenuity and patience, must try to help the pupil overcome his difficulties."—Peter C. Kronfeld

READING PROBLEMS IN HEMIANOPIA. Pameijer, J. K. (Deventer, The Netherlands), Ophthalmologica 160:322-325, 1970.

For left-sided hemianopia a black ruler placed at right angles and close to the beginning of the lines usually works well. A middle-aged patient with a right-sided hemianopia was aided by 1) turning the reading material 180 degrees so that the reading could be done from right to left, and 2) by inverting the now upside-down print by means of a Dutch telescope. (3 figures)—Peter C. Kronfeld

HISTOLOGY OF CONGENITAL GLAUCOMA. Manschot, W. A. (Rotterdam, the Netherlands), Ophthalmologica 160:326-329, 1970.

An eye with apparently congenital glaucoma was treated by cyclodiathermy when the patient was two years old, and with hypotensive medication from then on. Eight years later when the cornea was enlarged, globular and opaque, the fundus not visible and the pressure high, the blind, painful eye was enucleated. Histologically the canal of Schlemm was found to be open, its wall lined with endothelium and its intrascleral outflow channels patent. The canal was separated from the anterior chamber by a dense, sclerosed tissue which the author interprets as the compressed, hyalinized corneoscleral meshwork, damaged by the unrelieved pressure. The histological findings favor the view that goniotomy, even at this late stage, might have normalized the intraocular pressure. (2 figures, 6 references) —Peter C. Kronfeld

FLUORESCEIN ANGIOGRAPHY OF THE OPTIC DISC IN GLAUCOMA. Oosterhuis, J. A. and Gortzak-Moorstein, N. (Department of Ophthalmology, University of Amsterdam), Ophthalmologica 160:331-353, 1970.

Baseline values for normal fluorescence of the disc are provided by the typical large physiological cups of normal eyes. In the floor of these large cups fluorescein brings out a strikingly dense system of vessels which add up to more fluorescence than the vessels on the rim of the cup. In glaucomatous eyes the authors report diminished fluorescence of the disc which correlates roughly with the degree of glaucomatous cupping and with the restriction of the visual field. In patients with totally excavated discs and only small residual fields, fluorescence of the disc was absent. The color of the disc as judged by ophthalmoscopy (without fluorescein) can not be considered a reliable yardstick for its vascularization. (15 figures, 24 references)—Peter C. Kronfeld

X-RAY PHOTOS OF THE OPTIC FORAMEN. Bleeker, G. M. (X-ray Department of the University Eye Hospital, Amsterdam), Ophthalmologica 160:354-368, 1970.

Reliable pictures of the optic foramen can only be obtained when the central beam of the X-ray tube coincides with the axis of the canal which, in the normal skull, forms an angle of 37° with the sagittal plane and of 30° with the line joining the external auditory meatus with the inferior orbital rim. In pictures taken in this manner the optic foramen appears in the infero-temporal area of the orbit. In a series of pictures of the same patient the effect of slight deviations from the proper position of the head are demonstrated. Right-to-left size differences of 1 mm or more are usually significant, the larger foramen usually being the one altered by a pathological process. (23 figures)—Peter C. Kronfeld

AN UNNECESSARY MISTAKE. Planten, J. T. (Leeuwarden, the Netherlands), Ophthalmologica 160:369-371, 1970.

In three cases reported by the author opacities of the media precluded ophthalmoscopic examination of the posterior segment. When acute glaucoma developed and resisted conservative therapy, the author performed iridencleises on two of the patients, finding the iris unusually friable and the postoperative course longer than usual. In these two and in a third unoperated case the primary disease proved to be a malignant melanoma of the choroid. (2 figures)—Peter C. Kronfeld

NORRIE'S DISEASE. Hamburg, A. (Bussum, the Netherlands), Ophthalmologica 160: 375-377, 1970.

The occurrence of this oculo-acoustico-cerebral degeneration in three sons from a Dutch family is reported. Bilateral blindness due to pseudogliomas was discovered shortly after birth. At the present time only the second boy, age five, shows a serious mental defect. The EEG of all three cases is abnormal in that it shows peaks which increase during sleep. A great-uncle of the mother died in a school for the blind at the age of 12 which is the only clue to a genetic origin of the disorder. (1 reference)—Peter C. Kronfeld

OPERATION FOR ECTROPION ASSOCIATED WITH ANOPHTHALMOS. Hagedoorn, A. and Keur, J. H. W. (University Eye Clinic, Wilhelmina Gasthuis, Amsterdam), Ophthalmologica 160:379-382, 1970.

Three double-armed sutures are inserted in the region of the lower fornix, passed through

the periosteum near the lower orbital rim, brought out through the skin and fastened there with tape. Very much like the von Hess sutures of ptosis, the sutures advocated by the authors give rise to strands of scar tissue which run in the same direction as the inferior tarso-orbital ligament and take on this ligament's lost function. (5 figures)—Peter C. Kronfeld

## Journal of Neurology, Neurosurgery and Psychiatry

Volume 33 April, 1970 Number 4

Spurious papilledema and visual field contraction after head trauma. Dale, R. T. and Galin, M. A. (Departments of Neurology and Ophthalmology of the New York Medical College), J. Neurol. Neurosurg. Psychiat. 33:166-171, Apr., 1970.

Two patients with bilateral papilledema after head trauma, without increased intracranial pressure are discussed. Bilateral contraction of the visual fields, apparently on a permanent basis, was noted in both patients. The pathophysiology is believed to be related to indirect injury to the optic nerve. (8 figures, 13 references)—Joel G. Sacks

Mucocoele of the sphenoidal sinus as a cause of recurrent oculomotor nerve palsy. Friedmann, G. and Harrison, S. (The Neuro-Otological Department, the National Hospital for Nervous Diseases, Queen Square, London W.C. 1.), J. Neurol. Neurosurg. Psychiat. 33: 172-179, Apr., 1970.

The neurological symptoms and signs in 40 cases of sphenoidal mucocoele have been reviewed. Of these, 23 cases had optic nerve involvement; 15 cases had oculomotor nerve involvement; 2 cases had trochlear nerve involvement; 4 had abducens nerve involvement; 38 had facial pain and 12 had exophthalmos.

Two cases recurrent oculomotor nerve palsy caused by a sphenoidal mucocoele are described. (5 figures, 2 tables, 48 references)—Joel G. Sacks

## Neurology

Volume 20 May, 1970 Number 5

Polymyoclonia with opsoclonus. McLean, D. R. (Neurological Unit, Boston City Hospital, Massachusetts), Neurology 20:508-512, May, 1970.

The case reported was 50 years old; this is the oldest patient reported with this syndrome. Persistent abnormal eye movements two years after the acute illness were a unique feature which had not been previously reported. (15 references)—Joel G. Sacks

Facial pulses in internal carotid artery occlusion. Fisher, C. M. (Massachusetts General Hospital, Boston, Mass.), Neurology 20:476-478, May, 1970.

Abnormal pulses may be felt about the orbit and in the region of the nasolabial fold in patients who have had occlusion of one or both internal carotid arteries. These abnormal pulses arise as the result of dilatation of the vessels that carry anastomotic flow from the branches of the external carotid artery into the distal internal carotid artery by the way of the ophthalmic artery and its orbital branches. (1 figure, 1 reference)—Joel G. Sacks

Unruptured aneurysm of the supraclinoid carotid artery. A treatable cause of blindness. Bird, A. C., Nolan, B., Gargano, F. P. and David, N. J. (Departments of Ophthalmology, Radiology and Neurology, University of Miami School of Medicine, Miami, Florida), Neurology 20:445-454, May, 1970.

Five patients with giant aneurysms arising from the supraclinoid portion of the internal carotid artery have been described. In four of them the initial complaint was loss of vision in one eye, and if not treated, this progressed to blindness within a few months. Three patients benefited from carotid clamping in the neck. Two patients with profound visual loss in the postoperative period eventually showed spectacular visual improvement. (5 figures, 1 table, 12 references)—Joel G. Sacks

## Annals of Internal Medicine

Volume 72 May, 1970 Number 5

Pseudotumor of the orbit and limited Wegener's granulomatosis. Cassan, S. M., Divertie, M. B., Hollenhorst, R. W. and Harrison, E. G. (Sections of Medicine, Ophthalmology, and of Surgical Pathology, Mayo Clinic and Mayo Foundation; and the Mayo Graduate School of Medicine, Rochester, Minn.), Ann. Intern. Med. 72:687-693, May, 1970.

A patient with bilateral orbital pseudotumor and bilateral cavity pulmonary lesions is reported. This patient was considered to have the limited form of Wegener's granulomatosis that has been described recently, and his 15-year survival with this disease when last seen is unequaled in the literature. Orbital pseudotumor and its relationship with multifocal fibrosclerosis, polyarteritis nodosa, and Wegener's granulomatosis are reviewed. (6 figures, 40 references)—Authors' abstract

## Aerospace Medicine

Volume 41 April, 1970

Aftereffects of various alcoholic beverages on positional nystagmus and coriolis acceleration. Ryback, R. S. and Dowd, P. J. (USAF School of Aerospace Medicine, Brooks Air Force Base, Texas 78235), Aerospace Med. 41:429-435, April, 1970.

Bourbon appears to have a stronger effect than vodka on positional nystagmus and coriolis acceleration (that occurring when the head is tilted relative to a plane of rotation). (5 figures, 3 tables, 38 references)—Stan Muenzler

## Journal of Pediatrics

Volume 77 July, 1970

Microcirculation in young adults with cystic fibrosis: retinal and conjunctival vascular changes in relation to diabetes. Chazan, B. I., Balodimos, M. C., Holsclaw, D. S. and Shwachman, H. (The Children's Hospital Medical Center; and the Departments of Medicine and Pediatrics, Harvard Medical School), J. Pediatrics 77:86-92, July, 1970.

Conjunctival biomicroscopy and retinal photography were utilized in 67 patients with cystic fibrosis, ages 15 to 26 years, to detect a possible prediabetic vascular change. Examination revealed venular congestion and tortuosity as well as venular and arteriolar red cell aggregation. These changes were related to the severity of the cystic fibrosis and not to glucose intolerance. Both clinical and chemical diabetes occur more frequently in older patients with cystic fibrosis than in normal subjects. The diabetes is not related to the severity of the cystic fibrosis. A prediabetic vascular change could not be reliably detected by this study. (2 figures, 1 table, 32 references)—Authors' abstract

# NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
*700 North Michigan Avenue, Chicago, Illinois 60611*

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### CLINICAL CONGRESS: AMERICAN COLLEGE OF SURGEONS

The 57th annual clinical congress of the American College of Surgeons will be held in Atlantic City, New Jersey, on October 18-22, 1971. The postgraduate course in ophthalmic surgery will be offered on October 18th, 20th, and 22nd, under the direction of Robinson D. Harley of Philadelphia.

For further information contact Mr. T. E. McGinnis, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611.

### SOCIETY OF CONTEMPORARY OPHTHALMOLOGY

The winter meeting of the Society of Contemporary Ophthalmology will be held on February 27 through March 3, 1972, at the Diplomat Hotel, Hollywood, Florida.

The emphasis of the meeting will be on contemporary ophthalmology through continuing education. Lectures will be presented by the permanent faculty. Ophthalmologists interested in presenting papers on new material must submit a 150-word, titled abstract before October 1, 1971, to John G. Bellows, M.D., 30 North Michigan Avenue, Chicago, Illinois 60602.

### SECOND INTERNATIONAL OPHTHALMIC MICROSURGERY MEETING IN SAN FRANCISCO

The Eye Foundation of California will sponsor the second international ophthalmic microsurgery meeting, to be held on September 15-18, 1971, in San Francisco. The first two days of the meeting will be devoted to practical microscopic instruction at the San Francisco Eye and Ear Hospital. Lecturers for this session include F. Barraquer, Bogata, Colombia; J. Beale, U.S.A.; Prof. J. Draeger, West Germany; and E. Smith of Canada. The last two days of the meeting will be held at the Fairmont Hotel, and will consist of presentations, short papers, movies, and panel discussions. Lecturers will include J. Boberg-Ans, Denmark; Charles Kelman, U.S.A.; E. Malbran, Argentina; and R. Troutman, U.S.A.

The Foundation Gold Medal Award for World Eye Surgical Excellence will be presented to Ramon Castroviejo during the second portion of the congress.

Fees for both sessions will be $425, while the fee for the last two days alone will be $100. In either case, the additional fee for wives is $25.

Further information may be obtained from John Beale, San Francisco Eye and Ear Hospital, 1801 Bush Street, San Francisco, California 94109.

### CONTINUING EDUCATION IN OPHTHALMOLOGY

The American Academy of Ophthalmology and Otolaryngology program of continuing education includes an ophthalmic basic and clinical science course. The course presents a core of ophthalmic information divided into eight sections. Each section consists of an essential reading list, designed for completion in a period of two or three months

The registration is $50. For application and information contact C. M. Kos, M.D., Executive Secretary-Treasurer, American Academy of Ophthalmology and Otolaryngology, 15 Second Street SW, Rochester, Minnesota 55901.

### ESTELLE DOHENY EYE FOUNDATION

The annual postgraduate conference of the Estelle Doheny Eye Foundation will be held on October 18-19, 1971, in Los Angeles. Principal speakers will be Ramon Castroviejo and Frank W. Newell.

Further information may be obtained from the Estelle Doheny Eye Foundation, 272 South Lake Street, Los Angeles, California 90057.

### PLASTIC AND CORNEAL SURGERY SYMPOSIUM: BASCOM PALMER EYE INSTITUTE

The Bascom Palmer Eye Institute of the University of Miami School of Medicine, and the Florida Lions Eye Bank at Miami, announce the fourth biennial symposium on ophthalmic plastic and corneal surgery, to be held on March 26-31, 1972, at the Diplomat Hotel, Miami Beach, Florida.

Additional information may be obtained by writing to the Ophthalmic Plastic Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 875, Biscayne Annex, Miami, Florida 33152.

### OPHTHALMOLOGISTS SERVE PROJECT HOPE IN WEST INDIES

Ophthalmologists Hansjoerg Kolder, Iowa City, Iowa, and Edward A. Dunlap, New York City, have joined the staff of the hospital ship SS HOPE while this floating medical center is docked in Kingston, Jamaica, to carry out a 10-month medical and teaching mission in the West Indies which began in mid-January.

This is the SS HOPE's second decade of service. Approximately 125 staff members are serving for the entire voyage; Drs. Kolder and Dunlap joined more than 20 other specialists who serve for two-month periods.

Dr. Dunlap, who joined the staff of the hospital ship in March, is a clinical professor of ophthalmol-

ogy and acting division head of the New York Hospital-Cornell Medical Center. He has previously served with the SS HOPE in Ecuador and Ceylon.

Dr. Kolder, who joined the ship's staff in May, is associate professor of ophthalmology at the University of Iowa in Iowa City.

### Postgraduate Institute: New York Eye and Ear Infirmary

The Postgraduate Institute of the New York Eye and Ear Infirmary announces the 14th in a series of postgraduate courses for specialists in ophthalmology to be presented October 4 through December 11, 1971.

The following courses will be offered: diagnostic ultrasonography, pathology, uveitis, ocular geriatrics, ocular radiology, neuro-ophthalmology, motor anomalies, perimetry, biomicroscopy, ophthalmoscopy, radioisotopes in ophthalmology, fluorescein angiography, reading disability, indirect ophthalmoscopy, ocular adnexal pathology, ocular therapeutics, practical applanation tonometry, glaucoma, tonography and applanation tonometry, refraction, enucleation and evisceration, corneal contact lenses, plastic eye surgery, surgery of the orbit, lacrimal sac surgery, microsurgery in glaucoma, microsurgery of the cornea, microsurgery in cataracts, clinical perimetry and review in basic subjects in ophthalmology.

For a catalogue and further information contact Jane Stark, registrar, Postgraduate Institute, New York Eye and Ear Infirmary, 310 East 14th Street, New York, New York 10003.

### Safety lens now mandatory

Effective December 31st, 1971, the Food and Drug Administration requires that all eye glasses sold thereafter must have impact-resistant lenses.

The FDA issued the ruling with encouragement from the National Society for the Prevention of Blindness, but with opposition from the American Optometric Association.

More than 75 manufacturers and distributors of sun glasses requested postponement of at least a year, but FDA Commissioner Charles C. Edwards said the December 31st deadline gives the industry enough preparation time.

In first proposing the rule last September 30, Edwards said use of impact-resistant glass or plastic would increase the price of a pair of prescription glasses by between one and six dollars, but that it would help prevent many of the 120,000 injuries caused each year by broken lenses.

The final rule, published in the Federal Register, May 15, states that impact-resistant lenses are safer than ordinary lenses but still "not shatterproof or breakproof," a fact that the FDA said every wearer should be told. The National Society for the Prevention of Blindness had urged adoption of the rule as "one of the most important advances in the promotion of eye safety to date."

### Surgery Course: New York Eye and Ear Infirmary

A two-day course on dissection of the orbit, ocular adnexae, facial structures, and chiasmal area on individually assigned cadavers, with special emphasis on lacrimal, orbital, and eyelid plastic surgery, will be held at the New York Eye and Ear Infirmary on October 23-24, 1971. The course is under the direction of Lester T. Jones in association with Harold Kirshner. Enrollment is limited. The fee is $100.

For additional information contact Jane Stark, registrar, Post Graduate Institute, New York Eye and Ear Infirmary, 310 East 14th Street, New York, New York 10003.

### University of Texas at Galveston

The department of ophthalmology at the University of Texas Medical Branch at Galveston held its fifth annual postgraduate and alumni meeting on April 3, 1971. Marshall Parks was guest speaker.

The alumni association elected R. Sloan Wilson president, and Charles Broman secretary-treasurer for the coming year. Gaynelle Robertson, who retired in January, was presented with a golden apple award for his years of dedicated service to the department in the field of ophthalmology.

### Orbital Symposium: New York Medical College

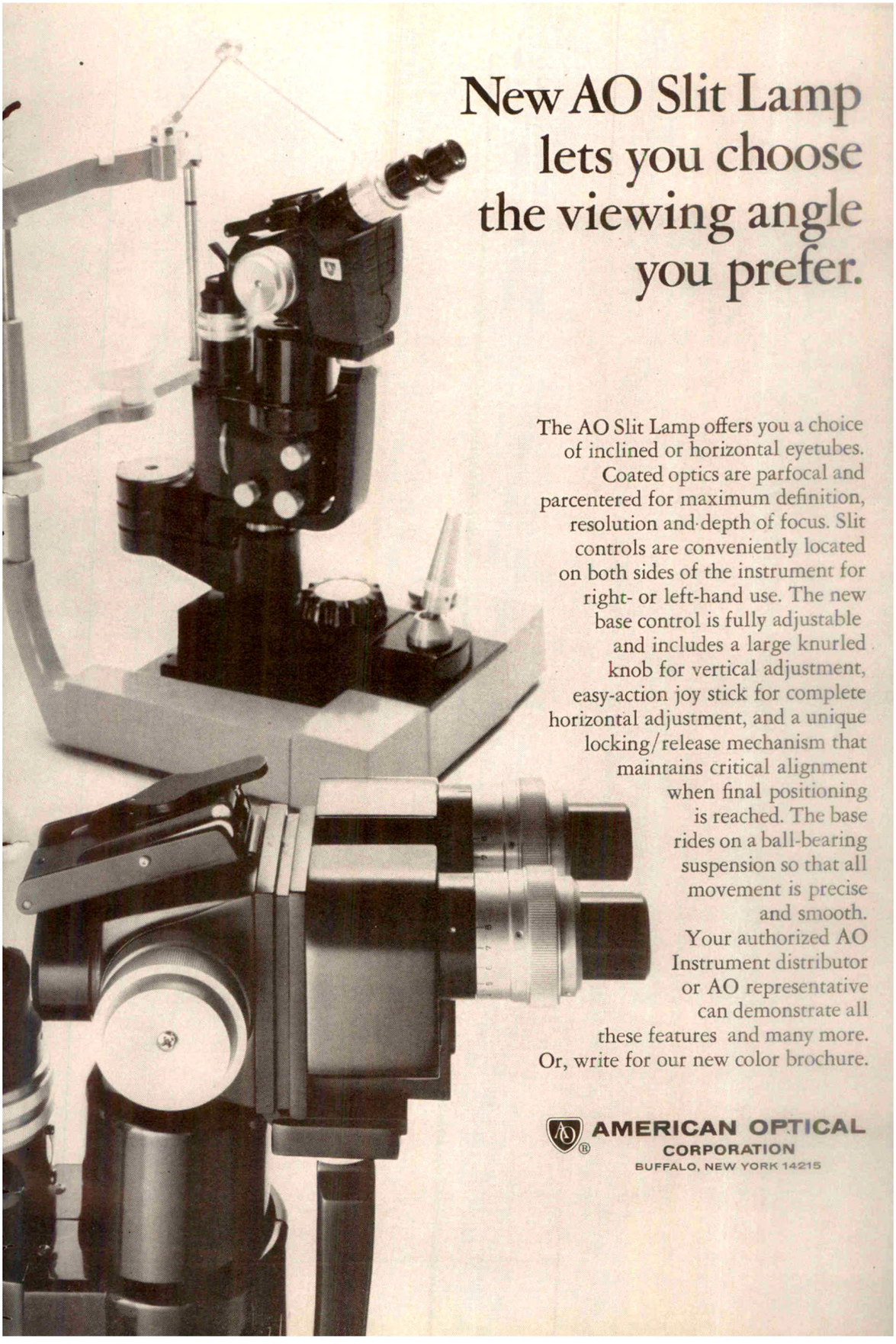
The department of ophthalmology of the New York Medical College announces a one-day orbital symposium October 30, 1971. Speakers will include members of the faculty as well as guests.

Preregistration is required. Registration forms, together with a program of the meeting, may be obtained from Mrs. Ruth Green, Department of Ophthalmology, New York Medical College, 1249 Fifth Avenue, New York, New York 10029.

## Personal

### Jules François

The first distinguished service honorary medal of the American Society of Contemporary Ophthalmology was presented to Jules François, professor of ophthalmology at the University of Ghent, Belgium, at the society's annual meeting, March 4-6, 1971, in Hollywood, Florida. Prof. François was selected by the governing board of the society for his outstanding contributions and excellence in ophthalmology. He has also been the recipient of the Gonin Medal and the Alfred Vogt prize, and is past president of the Royal Academy of Medicine of Belgium, Doctor Honoris Causa of six universities, and is a member of the Committee for the International Conference on Human Genetics.



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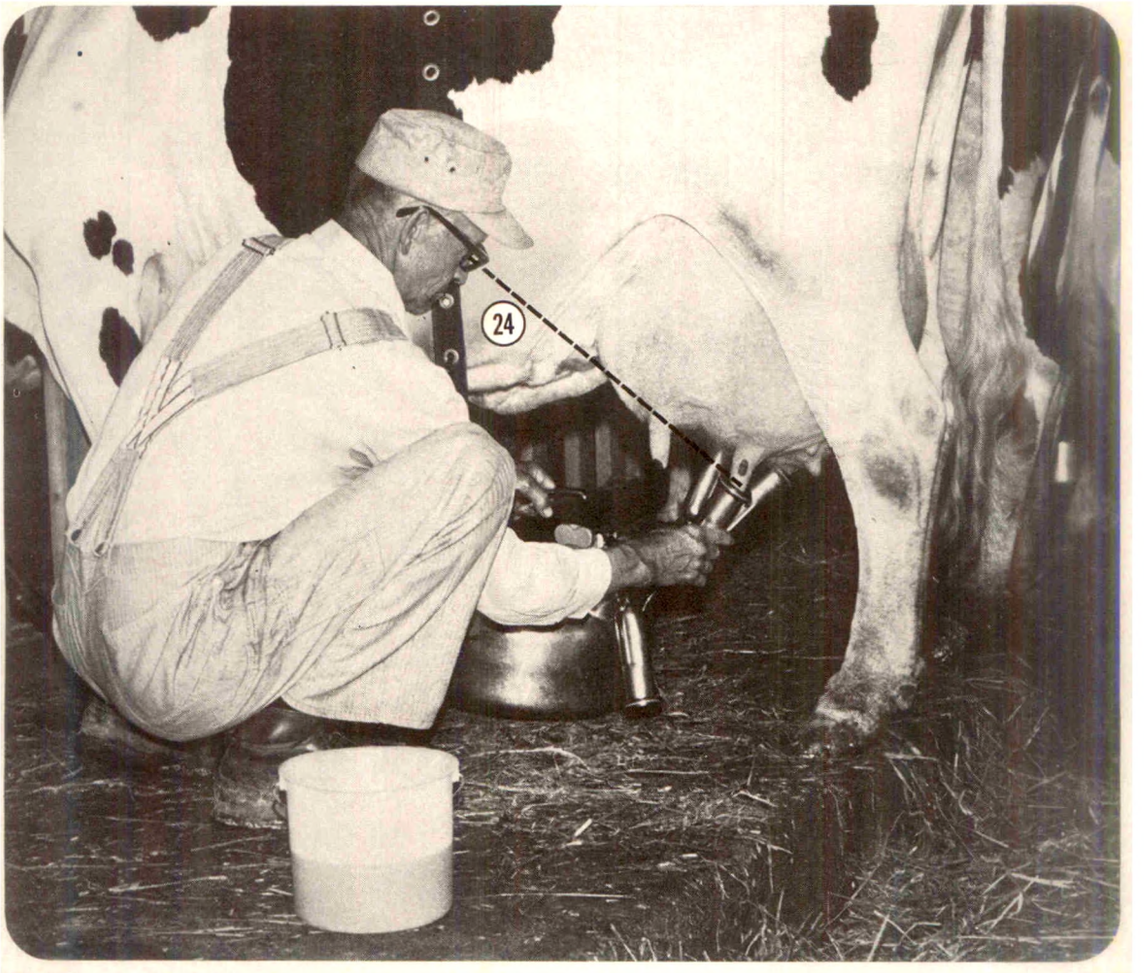
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# Dairy farmer

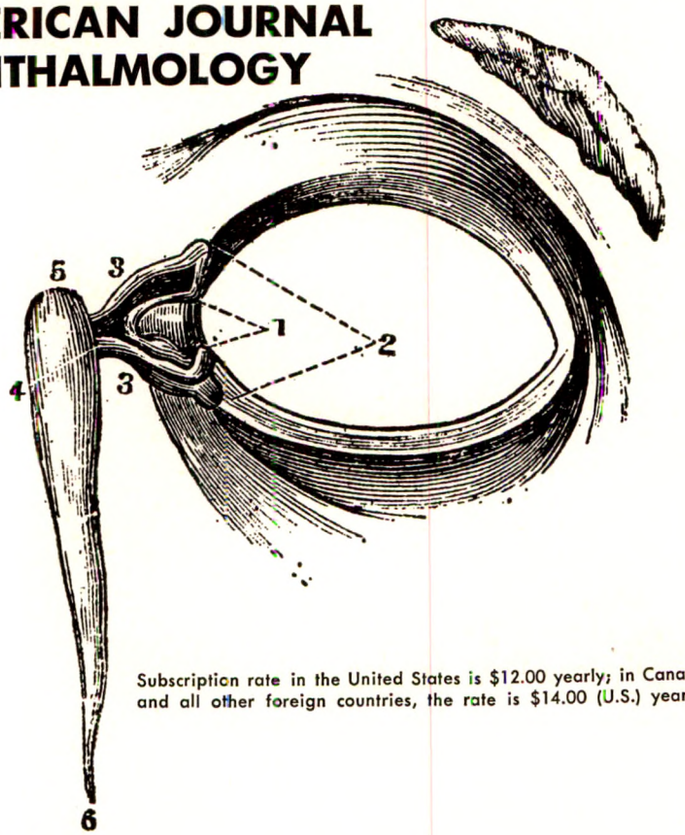
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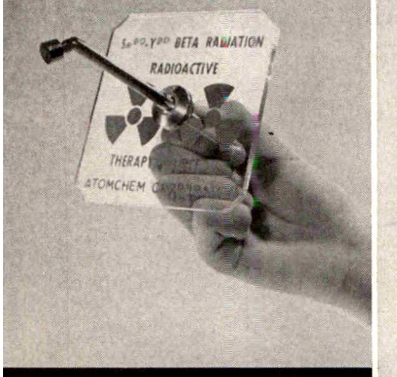
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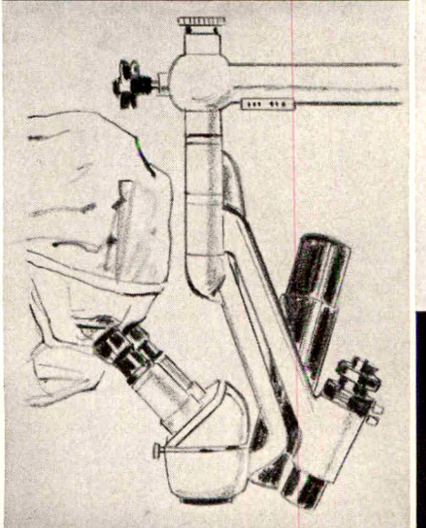


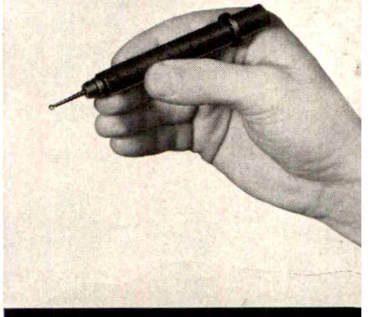

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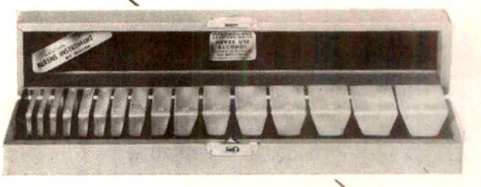
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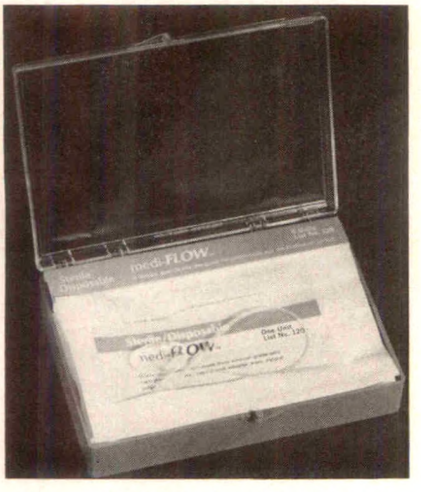
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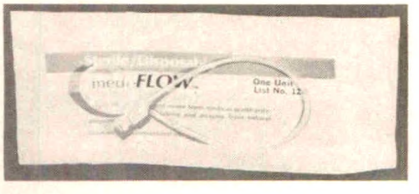


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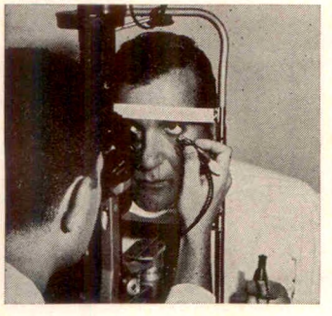
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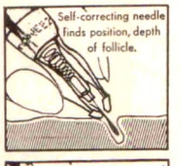
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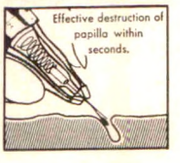
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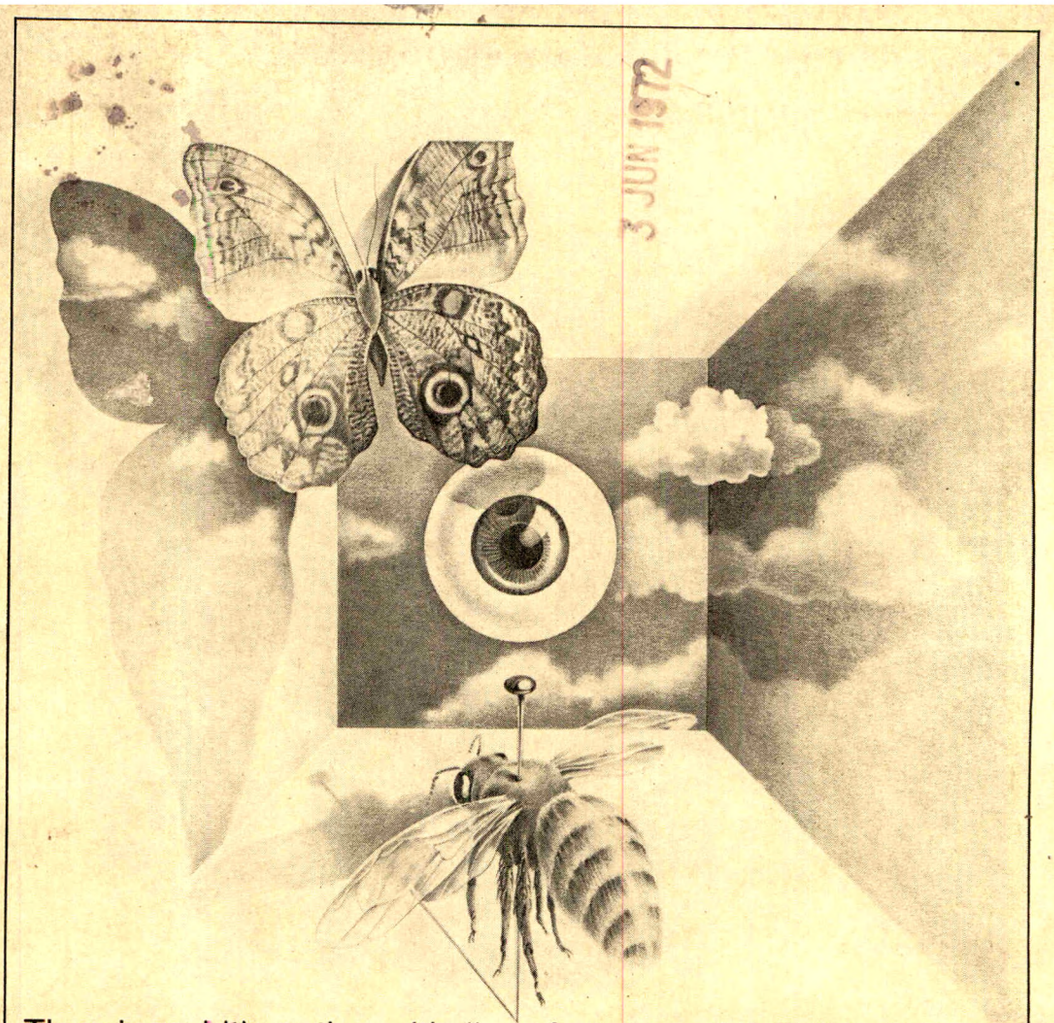
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# THE CORNEAL GRAFT

## A MULTIPLE VARIABLE ANALYSIS OF THE PENETRATING KERATOPLASTY

THOMAS E. MOORE, JR., M.D., AND SAMUEL B. ARONSON, M.D.

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THOMAS E. MOORE, JR., M.D., AND SAMUEL B. ARONSON, M.D.

*From the Departments of Ophthalmology, University of California School of Medicine at San Francisco, San Francisco General Hospital, the University of California Hospitals, and the Franklin Hospital Medical Center.* *This investigation was supported in part by USPHS Research Career Development Award K3 EY31 (Dr. Aronson), 653, and USPHS Grant EY 00246, EY 00408, and by Eyeitis.*

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## DEDICATION

This monograph is dedicated to the memories of Arthur George Leigh, M.D., F.R.C.S., and Jerome Deutschberger, M.A., whose influence and counsel were in a profound sense responsible for the nature and scope of this work.

George Leigh was senior ophthalmic surgeon at Moorfields Eye Hospital, and consultant ophthalmic surgeon at St. Mary's Hospital, London, England. Jerry Deutschberger was assistant chief of the Office of Biometry, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

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THOMAS E. MOORE, JR., M.D., AND SAMUEL B. ARONSON, M.D.

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THOMAS E. MOORE, JR., M.D., AND SAMUEL B. ARONSON, M.D.
*San Francisco, California*

Since the early period of keratoplasty, ophthalmic surgeons have anticipated a good outcome in the grafting of any diseased cornea. In the past, success could be attained only in patients with good prognosis. To maximize the possibility of success, we attempted to identify and define accurately the operative variables associated with graft failure.

Early in this attempt, it became evident that variables could be subdivided into two general groups according to time of occurrence: (1) the period of early graft reaction, and (2) the delayed reaction period. The early period (Fig. 1) extended from the time of surgery until suture removal. Arbitrarily selected variables in this period were: (1) selection of the donor graft tissue, (2) therapeutic protocols before and after surgery, (3) adjunctive medical therapy in the postoperative period, and (4) standardization of surgical technique to permit classification of each procedure. Variables evaluated and compared include: (1) morphologic status of the host eye, (2) etiologic and syndromal diagnosis of the host eye, (3) surgical procedures, (4) suture materials and techniques, (5) microbially-induced reactions, (6) immunologic status of the host, and (7) tissue noncompatibility. The variables found to be essential in the early graft period were: (1) morphologic classification, (2) surgical procedure, and (3) suture material.

Reprint requests to Thomas E. Moore, Jr., M.D., Suite 309, 45 Castro Street, San Francisco, California 94114.

The period of delayed graft reaction begins when the early graft reaction ends and extends indefinitely. Variables in this period include: (1) microbiology of the external eye, (2) immunologic factors in the host response, (3) pre- and postoperative morphology of the host eye, and (4) socioeconomic status of the recipient. Morphologic structure and socioeconomic status proved to be the critical variables in delayed graft failure.

The combination of early and delayed graft results makes up the long-term graft results for this series. Patients have been followed for a maximum of five years, so that definite long-term prognoses cannot be presented. However, the incidence of delayed graft reaction appears to diminish with time, so that reasonable projections can be made.

To evaluate clinical variables more extensively simultaneous studies were done in the rabbit. The early graft period was designated arbitrarily at 75 days, although sutures were removed between 10 and 14 days. Such early suture removal was required if a successful graft was to be achieved. The variables studied in this period were: (1) the surgical procedure, (2) suture toxicity, (3) pathogenic and indigenous bacterial toxicity, (4) tissue noncompatibility, and (5) genetic variability of the host. The factors of principal significance were: (1) the surgical procedure, (2) the suture material, and (3) genetic composition.

The delayed graft reaction was evaluated in rabbits 90 days following surgery. Delayed reactions were studied under both spontaneous and experimental conditions.

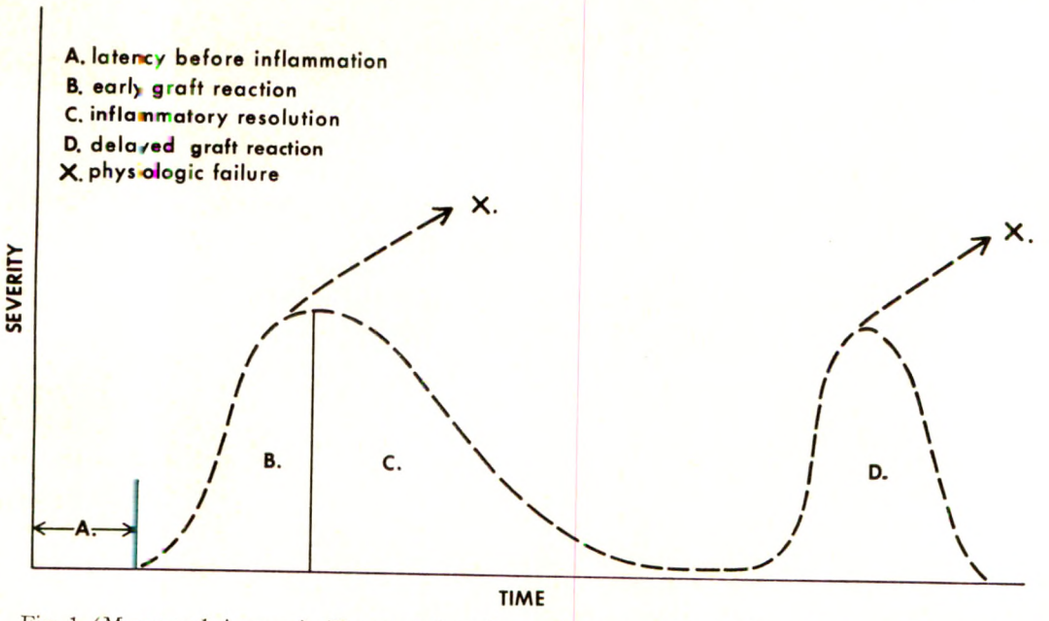



Fig. 1 (Moore and Aronson). The corneal graft reaction. The early graft reaction comprises periods B and C in a successful graft and B and X in graft failure. The delayed graft reaction comprises D in a successful graft and X in graft failure.

Variables evaluated include: (1) bacterial and antigenic stimuli, (2) immune competence of the host response, and (3) the severity of structural alteration. The rabbit graft experiments strongly support the observations made in the human series and provide a much more accurate appraisal of several factors in graft failure, e.g., the role of the tissue noncompatibility reaction. However, these observations cannot be used to verify aspects of the human data, but only to support it.

Finally, a large number of variables have been analyzed by discriminant function. This procedure provides statistical evidence to support some of our observations, e.g., the surgical procedure and suture toxicity. Similarly, it demonstrates that others are not statistically valid, e.g., immunologic evaluation. The strength of this technique is that an independent evaluation has utilized prospective data from our graft series and has placed in perspective the importance of each studied variable.

Although these studies have fallen somewhat short of our projected goal—namely, to graft successfully *any* vision-reducing cornea—they present an integrated approach to the corneal graft whereby that goal can one day be reached.

## HISTORICAL REVIEW

Historically, corneal grafting may be divided into two periods. The first period, or period of feasibility, extended from approximately 1844 (Kissam[1]) until approximately 1950.

In the early period, physicians sought to establish a satisfactory technique. During the 19th and early 20th centuries, there was a series of initial attempts, including the first clinical report[1] describing a xenograft from pig to man. The second period extends from 1950 through the present.[2] Power[3] reported allografts in a series of animal experiments in 1872; however, distinct confirmation of the basic principle of tissue noncompatibility was not readily accepted until the reports by Medawar on skin rejection in 1946[4,5] and those by Billingham and Boswell,[6] and by Maumenee,[7] that dealt specifically with the grafted cornea. Although many attempts to implant artificial materials (keratoprosthesis) were undertaken during this period, none met with success.

Implementation of a reproducible surgical technique was hampered considerably by the quality of instruments and suture material during the early period. Reported preferences for the trephine (round graft),[8] the double knife (square graft),[9] and the free-hand graft reflect the primitive technology of instrument-making. Crudeness of suture and needles during this period dissuaded the surgeon from using direct appositional techniques and favored overlay fixation. This obviously affected the results of the keratoplasty procedure.

The reason for the emergence of the lamellar keratoplasty as the procedure of choice during this period is obscure. Undoubtedly, the techniques for preparation and preservation of the donor cornea adversely affected the outcome of penetrating grafts. This problem was compounded by the technical problems of the period and the lamellar graft emerged as the favored procedure, as this enabled the surgeons to avoid the risks of intraocular surgery. Large series of lamellar graft results were assembled by surgeons between 1930 and World War II.[10,11]

The final factor of importance during this period was the suppurative infections that occurred following many graft procedures.[12,13] Inadequacies in managing these severe inflammatory reactions often led to phthisis bulbi, glaucoma, and enucleation. These complications caused the corneal surgeon to hesitate in undertaking a graft procedure. Whether these reactions were usually due to pathogenic bacteria is unknown; however, the advent of antibiotics seems to parallel the decline of such reactions.[2]

Since World War II, advancements in corneal grafting have been rapid. Several events contributed to this advancement.

First, the problems of instrumentation, suture, and pathogenic infection were surmounted, thus eliminating many of the technical difficulties of reproducible corneal surgery. The combination of the operating microscope,[14-16] microsurgical instruments,[17,18] and fine suture material and needles,[19] allowed reproducible, direct appositional suturing in penetrating keratoplasty. Wound dehiscences, or the "slipped grafts," are now infrequently seen, so that emphasis on a good visual result has made the penetrating graft preferable to the lamellar graft.

Perhaps of equal, if not greater, importance has been increased understanding of corneal physiology. Various reports[20-22] emphasized the importance of precise methods for donor cornea selection, especially with respect to age and history of corneal disease. Similarly, the length of time that a viable donor cornea can be retained at 4°C was determined. The establishment of eye banks was of particular importance in this regard; through them, an adequate number of viable donor corneas became available to the corneal surgeon.[23-25]

Studies of the vital role of the corneal endothelium and its effect on corneal hydration have exerted a major influence on selection

and handling of the donor cornea at surgery.[26-30] Evidence for persistence of the endothelium throughout the life of the graft[29-32] has convinced the surgeon of the necessity for extreme caution in the handling of the donor graft. The donor cornea is no longer placed in a holder with the endothelium facing downward before being placed in the recipient eye, a procedure which frequently compromised the endothelium. Now, every effort is made to avoid damage to the endothelium.

Since the end of World War II, the various factors involved in host acceptance or rejection of allogeneic tissue has been a major topic of investigation. Power[3] demonstrated the superiority of the allograft over the xenograft in animal experiments. Medawar[4-5] introduced the concept of histocompatibility within a given species. In skin grafting experiments within a species, rejection occurred if donor and recipient were not genetically histocompatible. While this reaction was not as severe as with heterologous tissue, it led to destruction of the donor tissue nonetheless.

Applied to corneal surgery, graft rejection was expressed as the "second set" reaction.

At some interval after having received a corneal graft, the host animal receives a skin graft from the same donor animal. The corneal graft subsequently undergoes a graft reaction.[33,34] This phenomenon was explained by the assumption that "skin immunization" stimulated immunologic components to react with the tissue of the donor cornea. Although similar reactions have been reported in man,[35,36] a direct relationship to an immune event has not been established.

Attempts to identify specifically the site of tissue antigenicity have been generally unsuccessful.[37-39] All layers of the cornea appear to demonstrate allogeneic antigenicity.[40,41] Many corneal surgeons remove the epithelium from the donor cornea before grafting.[42]

Other experiments on tissue incompatibility indicate that the cornea is less antigenic than skin, kidney, and heart.[43,44] When grafting experiments in rabbits are controlled for allograft variables, the incidence of tissue incompatibility is small regardless of the type of graft. Many workers have indicated that when such reactions do occur, they can be easily controlled with corticosteroid.[45-47] Such observations in animals have led many observers to question the importance of tissue incompatibility in the human graft reaction.[48-49] Logically, tissue incompatibility should occur, yet it does not seem to represent a major cause of graft failure.

During the current period of corneal grafting, inflammatory reactions other than tissue incompatibility have not received adequate evaluation. The rules of precise surgery, prevention of infection, and meticulous control of the donor cornea in great part have sufficed to answer these questions. Perlon sutures alone, according to the experience of Harms[50] and Mackensen and associates,[51] improve graft results significantly.

Finally, the field of keratoprosthesis has again emerged as a substitute for allograft keratoplasty. A series of plastic procedures ranging from the insertion of membranes within the diseased cornea[52-54] to sophisticated composite apparatuses that allow for refractive correction to be added to the device[55-58] have become the subject of experimental studies. On the whole, these are reserved for eyes with extremely poor prognoses. It is still too early to evaluate their effectiveness.

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## METHODS

All patients were selected for keratoplasty by identical criteria and they came from three sources. The first group, from San Francisco General Hospital (SFGH), was composed almost entirely of indigent walk-in patients. The second group, from the University of California Hospitals (UC), was composed of both referrals and walk-in patients with fixed incomes. The third group consisted of private patients, principally those referred to one of us (T.E.M., Jr.) for corneal surgery. Although this last group was initially composed of patients of moderate incomes, after July 1, 1968, indigent patients were included as a result of Medicare and Medicaid legislation.

While we attempted to include every patient with visual acuity (VA) of less than 20/100 attributable to a corneal lesion the corneal disease which we categorically excluded from surgical consideration was severe keratitis sicca (xerophthalmia), primarily because we had no technique for maintenance of corneal epithelium following penetrating keratoplasty in such eyes. Other patients in whom surgery was considered contraindicated according to our criteria were: (1) those with systemic disease who were poor anesthetic or survival risks, and (2) those who were mentally disturbed. There were also a certain number of patients who refused surgery.

Graft results are expressed in terms of patients, eyes, and cases. This series was comprised of 133 patients and 144 eyes, but there were 163 cases, since some eyes were operated upon more than once. A "case" is a single penetrating keratoplasty, and since one eye in this series received three keratoplasties, it is listed, therefore, as three cases. Only 12 patients in this series required bilateral surgery. All operations were performed between April 3, 1965, and June 28, 1969.

Corneal disease was classified by clinical-morphologic, etiologic, and immunologic criteria. Primary bases for clinical and morphologic classification were: (1) presence or absence of corneal neovascularization, and (2) evidence of intraocular inflammation. Morphologic stages are categorized in six groups (Fig. 2), each demonstrating progressively severe structural change. The category: 0+ indicated corneal distortion from inflammatory disease, without scarring or neovascularization. Predominantly, patients in this category were those with keratoconus (Fig. 3-A) and those with familial dystrophies (Fig. 3-B), including Fuchs'. (Two patients in this category received allografts in clear corneas of blind eyes, when autografts were taken from these corneas to be placed in the second, sighted eye.) A classification of 1A+ indicated central stromal scarring without vascularization and intraocular inflammation, including contusive or lacerative lesions (Fig. 3-C). A classification of 1B+ indicated corneal opacity or scarring with a history of intraocular inflammation, principally composed of aphakic bullous keratopathy (Fig. 3-D). A classification of 2+ indicated superficial corneal scarring and neovascularization without active intraocular inflammation, most frequently composed of patients with previous microbial inflammation (Fig. 3-E). A classification of 3+ indicated deep corneal scarring, superficial and deep stromal vascularization, presumptively free of intraocular disease (Fig. 3-F). A classification of 4+ included 3+ patients with definite signs of inflammation, whether active or inactive (Figs. 3-G and 3-H). In certain cases, it was difficult to decide accurately to which one of these last two groups a patient should be assigned. Diagnoses in the last two groups were predominantly microbial infections, chemically-induced keratitis, and atopic keratitis (Figs. 3-F through 3-H). When possible, cases were initially classified twice—

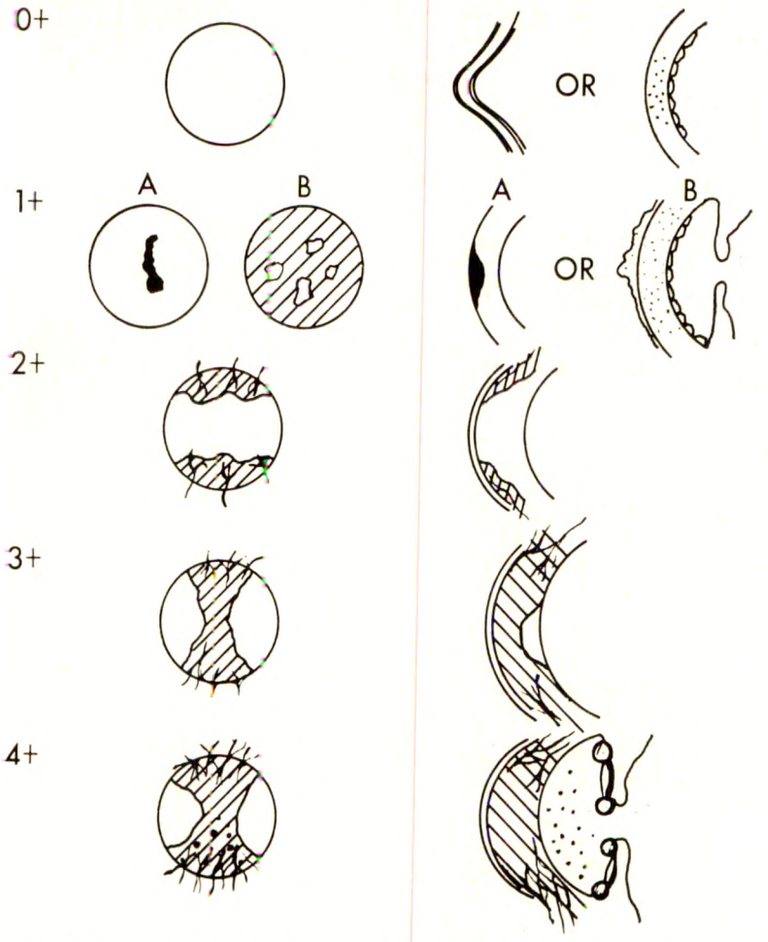



Fig. 2 (Moore and Aronson). Morphologic classification of corneal disease.

first during active inflammation, and then again after corneal inflammation subsided on combined corticosteroid and antimicrobial therapy.[1] Both of us (T.E.M., Jr., and S.B.A.) evaluated and classified each patient independently and then compared our results. When disagreement occurred we discussed our reasons for each designation and then reached a common decision (Table 1).

Classification by etiology or clinical syndrome included the following groups: (1) keratoconus, (2) familial corneal dystrophies (including Fuchs' dystrophy), (3) aphakic bullous keratopathy, (4) trauma, (5) herpes simplex keratitis, (6) herpes zoster keratitis, (7) bacterial keratitis, (8) idiopathic stromal keratitis, (9) physically or chemically induced keratitis, and (10) other diagnoses (Table 2).

Diagnosis of keratoconus, familial dystrophies, aphakic bullous keratopathy, trauma, and physical or chemical stimuli was based upon history and clinical morphologic evaluation. Herpes simplex keratitis required identification of an epithelial dendrite by an experienced observer, a positive culture, or identification by electron microscopy. Herpes zoster ophthalmicus was diagnosed on the basis of its peculiar dermatomal pattern (usually unilateral) with vesicular skin lesions. Bacterial keratitis was diagnosed by conjunctival culture. Other diagnoses included: (1) primary ischemic corneal necrosis,[2] (2) atopic keratitis, (3) interstitial ker-

atitis (syphilitic or idiopathic), (4) clear corneas for autograft, and (5) corneal leukoma secondary to sympathetic ophthalmia.

The etiologic and morphologic categories overlapped to some degree (e.g., aphakic bullous keratopathy was principally classified as 1B+, but herpes simplex keratitis was frequently 3 or 4+, Table 3).

Classification according to immunologic criteria involved evaluation of each patient by certain tests and subsequent comparisons of test results with the short- and long-term outcome of the penetrating graft. Tests were run several times during the period in which the patient was followed; these included preoperative evaluation, four to six months' postoperative evaluation, and re-evaluation at yearly intervals thereafter. Immunologic testing included: (1) protein electrophoresis, (2) qualitative immunoelectrophoresis, and (3) quantitative immunoglobulin determination for IgG, IgA, IgM, and early IgG. Quantitative values for any given patient over a prolonged period of time varied slightly, ranging between 10 to 15%. This was not true in patients with chronic systemic inflammatory disease; in these cases, there was usually a progressive increase in IgG.

Preoperative bacterial cultures were taken only when patients showed some signs of active corneal or external disease. Similarly, postoperative cultures were taken when bacterial origin of clinical inflammation was suspected. Cultures were plated on blood, chocolate, and mannitol agars, and evaluated for pathogenic and indigenous bacteria.

Preoperative therapy[3-5] was contingent upon classification and consisted of three general protocols: Group 1 consisted of patients with active central stromal keratitis (CSK), and these patients were assigned to a combined regimen of corticosteroid and specific therapy. Group 2 consisted of patients

TABLE 1

MORPHOLOGIC CLASSIFICATION OF CORNEAL DISEASE

| Category | Total Cases | Eyes | Patients |
|---|---|---|---|
| Early graft period | | | |
| 0+ | 32 | 32 | 23 |
| 1A+ | 1 | 1 | 1 |
| 1B+ | 17 | 11 | 11 |
| 2+ | 12 | 12 | 11 |
| 3+ | 34 | 31 | 31 |
| 4+ | 67 | 57 | 56 |
| Total | 163 | 144 | 133 |
| Long-term follow-up | | | |
| 0+ | 26 | 26 | 20 |
| 1A+ | 1 | 1 | 1 |
| 1B+ | 14 | 10 | 10 |
| 2+ | 12 | 12 | 11 |
| 3+ | 32 | 29 | 29 |
| 4+ | 61 | 51 | 50 |
| Total | 146 | 129 | 121 |

TABLE 2

ETIOLOGIC CLASSIFICATION OF CORNEAL DISEASE

| Category | Total Cases | Eyes | Patients |
|---|---|---|---|
| Keratoconus | 14 | 14 | 12 |
| Corneal dystrophy | 17 | 17 | 10 |
| Traumatic opacity | 6 | 6 | 6 |
| Aphakic bullous keratopathy | 30 | 26 | 26 |
| Herpes simplex | 37 | 31 | 31 |
| Herpes zoster | 5 | 5 | 5 |
| Bacterial ulcer | 7 | 7 | 7 |
| Idiopathic stromal keratitis | 26 | 21 | 20 |
| Physical or chemical agents | 13 | 10 | 10 |
| Physical | (2) | (1) | (1) |
| Chemical | (11) | (9) | (9) |
| Other diagnoses | 8 | 7 | 6 |
| Total | 163 | 144 | 133 |

TABLE 3

CORRELATION BETWEEN ETIOLOGIC AND MORPHOLOGIC CLASSIFICATIONS BY CASES

| Etiologic Classification | Morphologic Classification | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 0+ | 1A+ | 1B+ | 2+ | 3+ | 4+ | |
| Keratoconus | 14 | | | | | | 14 |
| Corneal dystrophy | 16 | | | | | 1 | 17 |
| Aphakic bullous | | | 17 | 1 | 4 | 8 | 30 |
| Trauma | | 1 | | 1 | | 4 | 6 |
| Herpes simplex | | | | 1 | 14 | 22 | 37 |
| Herpes zoster | | | | 1 | 1 | 3 | 5 |
| Bacterial keratitis | | | | 2 | | 5 | 7 |
| Idiopathic stromal keratitis | | | | 6 | 9 | 11 | 26 |
| Physical or chemical agent | | | | | 4 | 9 | 13 |
| Other diagnoses | 2 | | | | 2 | 4 | 8 |
| Total | 32 | 1 | 17 | 12 | 34 | 67 | 163 |

who presented with inactive CSK, and these patients received either corticosteroid alone or the combined regimen. Group 3 patients were those with a good prognosis and inactive CSK at presentation and they received no corticosteroid.

*Group* 1—Patients in this group were placed on hourly corticosteroid drops (prednisolone acetate 1% suspension), combined with the appropriate topical antimicrobial agent, usually in equivalent dosage—e.g., herpes simplex keratitis patients were treated with topical prednisolone acetate 1% drops, six A.M. to 10 P.M., with IUDR (Herplex) in matched dosage. Therapy was continued until active inflammation subsided.* If a central scar remained, and visual acuity was 20/100 or less, the patient was continued on hourly topical corticosteroid therapy until the time of surgery.

*Group* 2—Patients in Group 2, whose disease was inactive at the time of their initial presentation, were treated with topical corticosteroid hourly (prednisolone acetate 1%, six A.M. to 10 P.M.) for seven to 10 days before surgery. When herpes simplex was identified, the patient was also placed on a matched dosage of IUDR. Appropriate antibiotic therapy was used only following positive culture identification.

Groups 1 and 2 comprised the prophylactic corticosteroid series and included the first 95 patients.

*Group* 3—Patients in Group 3 were those considered to have a good prognosis, based upon a combination of morphologic and immunologic signs. They were not started on corticosteroid until they demonstrated evidence of postoperative inflammation.[5] In the last 45 cases of this series (Cases 118 to 163), all 45 grafts were sutured with 10-0 Ethilon (Ethicon) suture. The combined morphologic and immunologic classification is given in Table 4. Patients in the 0+, 1A+, 1B+, and 2+ morphologic categories (a total of 26 cases in Group 3) were not treated preoperatively with corticosteroid, but 3+ patients with $\leqq$8.0 units early IgG and 4+ patients with $\leqq$9.0 units early IgG (a total of 19 cases) were treated according to the preoperative treatment protocol. This schedule has markedly simplified the pre- and postoperative keratoplasty procedure in eyes with a good prognosis.

Donor corneas were selected from subjects between the ages of seven and 60 years who were without evidence of corneal

* In the past, if a patient's cornea perforated before inflammatory activity subsided, the procedure was immediate keratoplasty. Now, however, the procedure of choice is to cement a hard contact lens to the anterior cornea overlying the perforated area, using isobutyl cyanoacrylate adhesive.[6,7] Corticosteroid therapy is then continued until inflammation resolves sufficiently to allow surgery.

TABLE 4

PROTOCOL FOR PRE- AND POSTOPERATIVE CORTICOSTEROID THERAPY ACCORDING TO MORPHOLOGIC CLASSIFICATION

| Morphologic Group | Preoperative Corticosteroid | No Preoperative Corticosteroid |
|---|---|---|
| 0+ | | All |
| 1A+ | | All |
| 1B+ | | All |
| 2+ | | All |
| 3+ | <or=8.0 early IgG units | >8.0 early IgG units |
| 4+ | <or=9.0 early IgG units | >9.0 early IgG units |

disease on slit lamp examination. Infectious hepatitis was the only systemic diagnosis which excluded donor eyes. Eyes were enucleated within six hours of death and placed in moist chambers which were stored at 4°C. Most donor eyes were used within 24 hours, and never more than 42 hours, postmortem.

Before surgery, donor eyes were rinsed in an ophthalmic solution of polymyxin B, neomycin, and gramicidin (Neosporin), and then examined under the operating microscope for intrinsic defects in Bowman's and Descemet's membranes, or endothelial dystrophy. Only eyes free of intrinsic corneal pathology were used for keratoplasty.

Tissue or blood-group typing was not undertaken.

*Surgical procedure*—The surgery protocol was already well established. One of us (T.E.M., Jr.) was the surgeon in charge in every case, performing all the surgery in private cases and supervising every detail of the procedure in staff cases. In this way, the surgery was comparable in every case.

To evaluate the effect of surgical modifications over a given period, the series has been subdivided into four time intervals. During the first (1965–67) and second (1967–68) periods, interrupted silk suture was used; during the third period (1968–69), interrupted 10-0 nylon (Ethilon) suture was used; and in the last period (1969), continuous 10-0 Ethilon suture was used. Because of the change in suture material and suturing technique, only the first and second periods give an accurate comparison of the effect of experience on surgical results.

Almost every operation was done under general anesthesia. The techniques of anesthesia were relatively comparable. Hyperosmotic agents were used in aphakic cases and in combined procedures. Every procedure was performed under the Zeiss operating microscope or diploscope.

There were three fundamental surgical procedures: (1) a simple penetrating keratoplasty without an iridectomy, (2) a combined cataract extraction and penetrating keratoplasty with iridotomy or iridectomy, and (3) penetrating keratoplasty with anterior chamber revision. The last procedure included gross synechialysis, subtotal or total iridectomy, anterior and posterior membrane excision, cataract extraction, vitreous membrane excision and vitreous aspiration, and evacuation of hemorrhage. This group of cases was extremely heterogeneous and included patients who had had previous multiple surgery, massive trauma, and severe chemical burns. All of these patients were in the 4+ category and represented the poorest prognostic group of the entire series.

*Technique for simple penetrating keratoplasty*—The eye was secured with bridle sutures on all four rectus muscles. The area of the recipient cornea was measured. This usually encompassed the entire lesion; however, when the lesion extended to the limbus, it was transected with the corneal trephine. Once the graft size and position had been determined, a paracentesis wound was made with a Graefe knife. The donor button was denuded with a cyclodialysis spatula, care being taken not to damage Bowman's mem-

brane. The donor corneal button was trephined (Grieshaber-Franceschetti trephine), perforating the anterior chamber; the incision was completed with straight corneal scissors. Almost all corneal buttons in this series were between 7.0 and 8.0 mm in diameter, although they ranged in size from 6.5 to 10.0 mm.

Next, the recipient button was cut in the same fashion as the donor, except that no special effort was made to perforate the anterior chamber with the trephine. In combined procedures, peripheral iridectomies or iridotomies were performed in the 12, three, six, and nine o'clock meridians. The donor button was positioned and sutured in the same meridians. If interrupted sutures were used, three to six sutures were placed in each quadrant, totaling 12 to 24 sutures (e.g., 7.0 mm:12 sutures, 7.5 to 8.0 mm:16 sutures) per graft. If a continuous Ethilon suture was used, between four and six loops were placed in each quadrant. Sutures were inspected for accuracy of apposition and then they were tied. (The continuous nylon suture was tied in the 12 o'clock meridian with the knot buried beneath the bulbar conjunctiva.) The wound was inspected for watertight integrity and absence of anterior synechiae. When necessary, the anterior chamber was reformed, with balanced salt solution injected through the paracentesis wound. The pupil was dilated, the eye was double-patched, and the patient was taken to the recovery room.

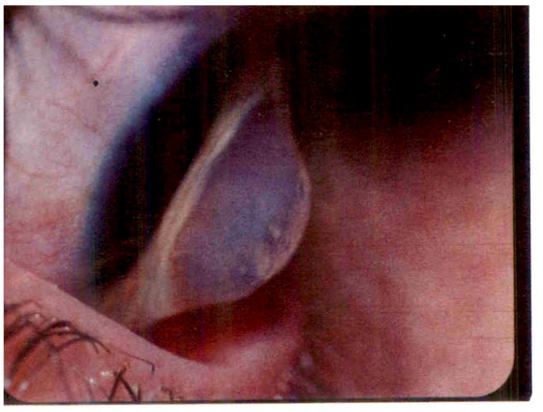
*Combined surgical procedure*—Combined keratoplasty–cataract procedures were done through the trephination wound. Anterior segment revisions, being extremely heterogeneous, cannot be described as a set format.

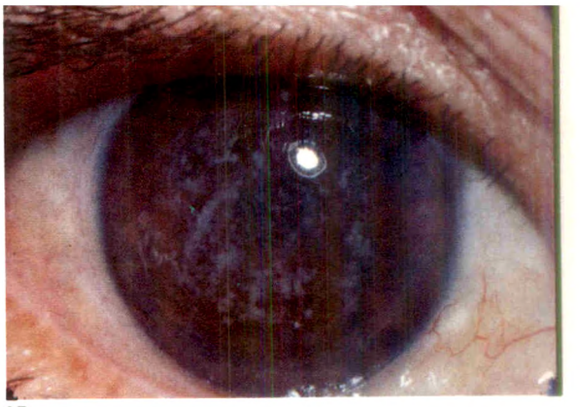
*Postoperative procedure*—Following surgery, the patient's operated eye remained double-patched for the first 36 to 48 hours. At the end of this period, active postoperative therapy was started. In Groups 1 and 2 this included hourly prednisolone acetate 1% drops from six A.M. to 10 P.M. for six weeks after surgery; at that time, the dosage was tapered and finally discontinued. In most cases, corticosteroid was discontinued by the second week after suture removal (about 18 to 22 weeks after surgery). Acetazolamide (Diamox), 1000 mg/day, and KCl, 20 mEq/day, were started simultaneously with topical corticosteroid as prophylaxis against corticosteroid-induced glaucoma. An ophthalmic solution (Neosporin) was given four times daily throughout the first week, and sulfisoxazole (Gantrisin) drops were given twice a day until suture removal. Mydriatic drops (phenylephrine 10%, cyclopentolate 2%) were also given twice daily for the first seven days and then only given symptomatically. In confirmed herpes simplex cases, topical IUDR was used in matched dosage with topical corticosteroids. Similarly, in bacterial keratitis, the appropriate topical antibiotic was used in matched dosage with the corticosteroid.

When glaucoma was present, the patient was maintained on antiglaucoma medication. (The sequence of topical medication which we have followed has been 1 to 4% pilocarpine, then epinephrine 1%, then phospholine iodide 0.125 to 0.25%, and finally oral glycerol,[8] approximately 1 g/kg.) If maximal

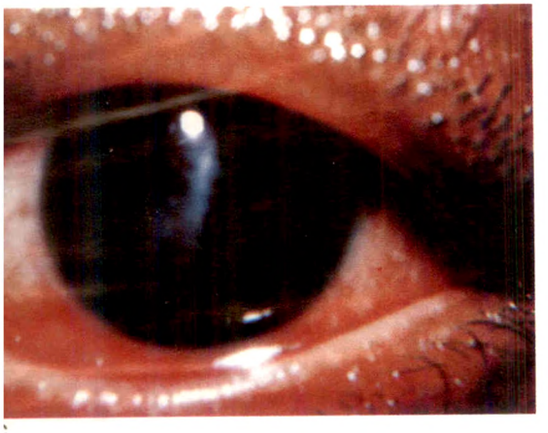
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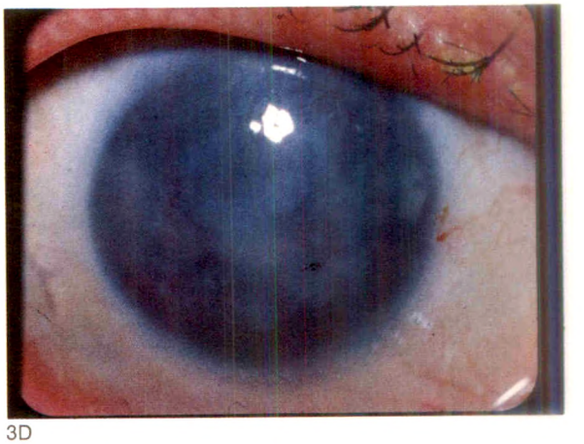
Fig. 3 (Moore and Aronson). Preoperative morphologic classification of corneal disease: (A) 0+ = keratoconus with severe hydrops. (B) 0+ = granular familial dystrophy. (C) 1A+ = corneal scarring secondary to corneal laceration. (D). 1B+ = aphakic bullous keratopathy. (E) 2+ = superficial stromal neovascularization secondary to herpes simplex. (F) 3+ = superficial and deep stromal neovascularization secondary to alkali injury. (G) 4+ = corneal leukoma with anterior chamber involvement secondary to variola. (H) 4+ = perforation of ocular contents through cornea and subsequent conjunctival flap (etiology —herpes simplex).



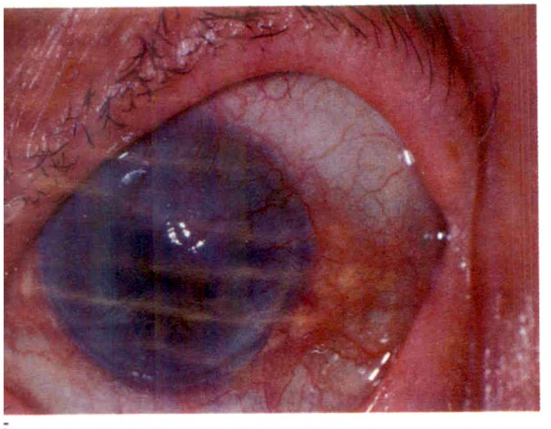


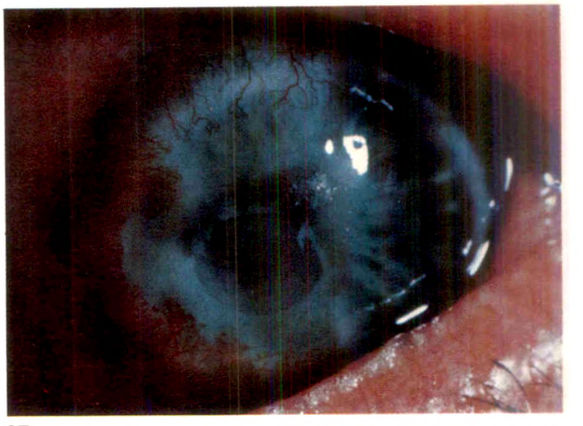
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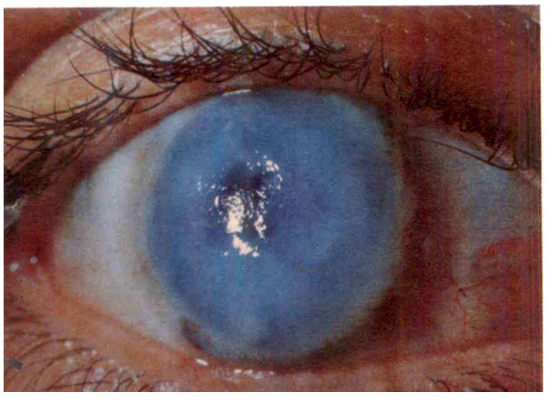


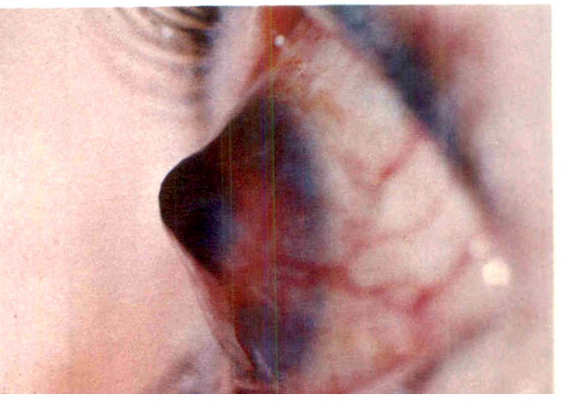
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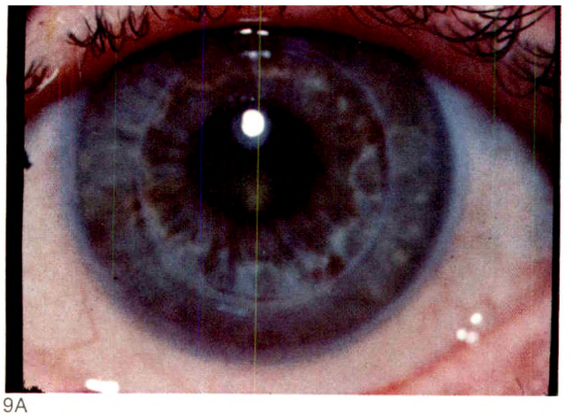




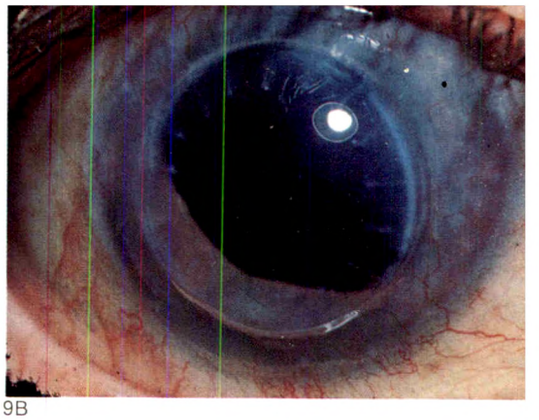
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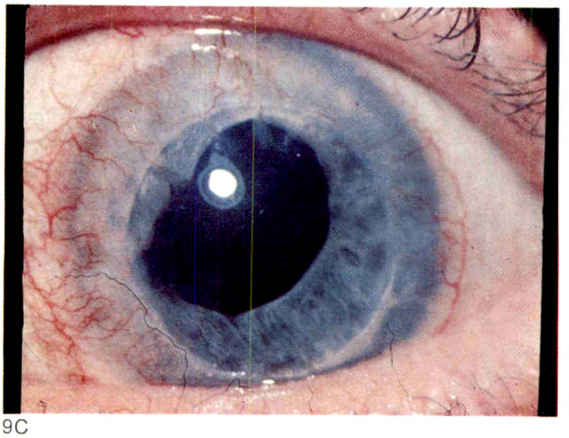




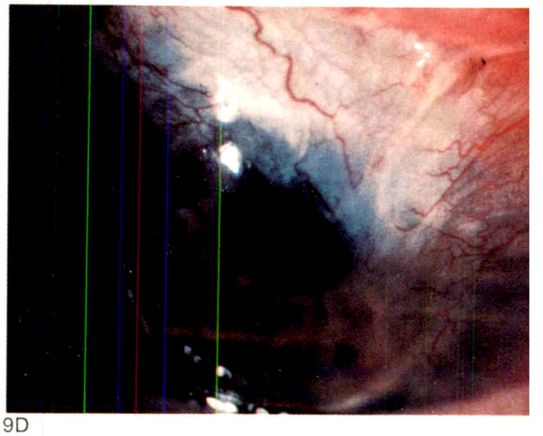
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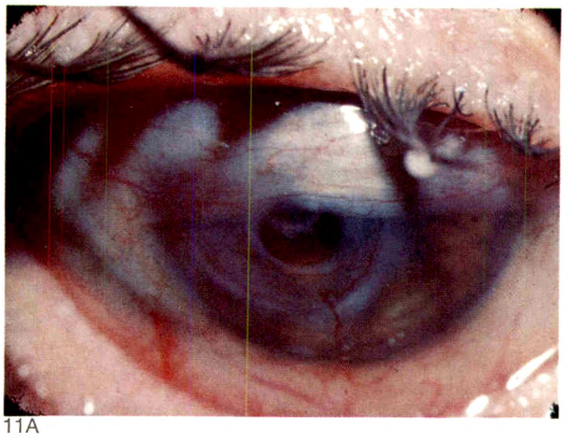
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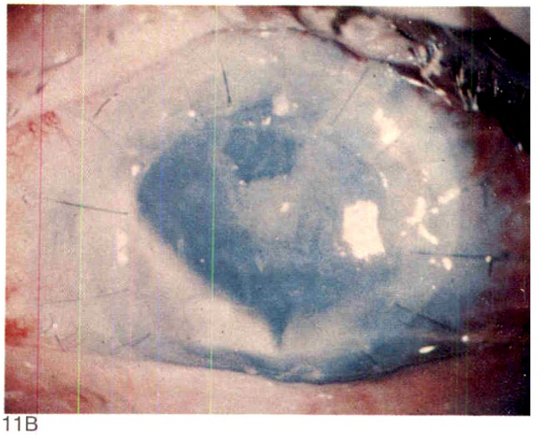
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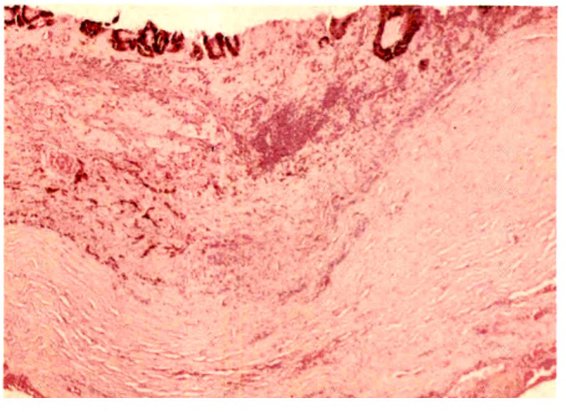
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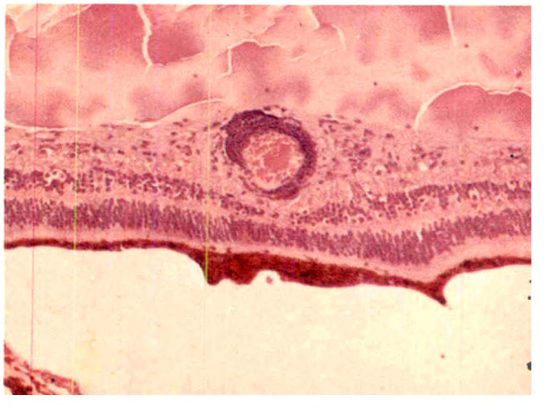


11A



11B





medical antiglaucoma therapy was not adequate, surgery was undertaken. All efforts were made to avoid further surgery, except in cases of acute angle-closure glaucoma; in all, only four cases required glaucoma surgery.

As noted, the protocol was revised for patients in the favorable immunomorphologic groups (Table 4). In this protocol, postoperative corticosteroid medication was only used on evidence of inflammation in the graft or anterior chamber. Hourly topical corticosteroids were then used until inflammation subsided. Antiglaucoma medications were used only in response to increased intraocular pressure. Antibiotics and mydriatics were used in the same fashion as in the first protocol.

When severe inflammation persisted even in the presence of hourly topical corticosteroids, daily or twice daily subconjunctival corticosteroids (0.8 ml dexamethasone, 4 mg/ml, and 0.2 ml xylocaine 2%) were administered in the area adjacent to the site of greatest activity until the reaction subsided. Similarly, if evidence of peripheral ischemia occurred,[2] subconjunctival heparin (500 mg) was employed every other day until revascularization occurred.

As a rule, private and UC patients were hospitalized from 10 to 20 days following surgery and examined daily by slit lamp. SFGH patients were usually hospitalized up to 12 weeks to ensure adherence to the postoperative protocol. Once discharged, patients were seen one to three times a week until sutures were removed. Following suture removal, the frequency of visits was gradually diminished to one visit every six months (Table 5). Patients were warned, however, that if they experienced blurred vision, photophobia, ocular pain, or redness, they must be seen immediately. Patients who lived at a distance were often seen by their referring ophthalmologist, who began therapy according to the protocol described below. If the patient did not respond within several days, he was sent back to us for evaluation and subsequent therapy.

When a delayed graft reaction was diagnosed, nonspecific and specific therapy were started immediately. In order to determine appropriate specific therapy, bacterial or viral identification was made by culture or pertinent clinical history.

The therapeutic regimen consisted of hourly topical prednisolone acetate 1% (Prednefrin Forte) from six A.M. to 10 P.M. to the involved eye, plus the appropriate

Fig. 9 (Moore and Aronson). A-F Microbial toxicity (early graft reaction). G-H. Tissue incompatibility (early graft reaction). (A) Patient 9, demonstrating severe pseudomonas infection. (B) Same patient following inflammatory inactivation with combined corticosteroid Polysporin therapy. (C) Same patient four days after surgery, demonstrating a pseudomonas, suture-tract abscess following penetrating keratoplasty. (D) Same patient 12 weeks after surgery, demonstrating a clear graft. Note area of corneal scarring in the eight o'clock meridian. (E) Patient 10, three weeks postsurgery, demonstrating inflammatory infiltrate and neovascularization around interrupted sutures. The continuous suture is free of reaction. (F) Same patient one week after removal of interrupted suture. Note involution of conjunctival neovascularization. (G) Patient 11, demonstrating graft failure seven months after surgery. (H) Same patient (high magnification). Note that many superficial and deep vessels enter the donor cornea between suture tracts.

Fig. 11 (Moore and Aronson). Postoperative morphologic classification. (A) Absent host neovascularization following keratoplasty in keratoconus. (B) Mild host neovascularization following grafting in aphakic bullous keratoplasty. Note superficial vessels in the host cornea at four and 10 o'clock positions. (C) Moderate host neovascularization following grafting in herpes simplex keratitis (3+). Note superficial and deep vessels throughout the host cornea. (D) Moderate host neovascularization following graft for alkali keratitis. Note sequential distribution of neovascularization.

TABLE 5

FREQUENCY OF OCULAR EVALUATION

| Time Period | Frequency of Visits |
|---|---|
| During hospitalization | Daily |
| As outpatient until suture removal | Two to three times a week |
| Three to six months | Once a month |
| Six months to one year | Once every three months |
| One to two years | Once every six months |
| Thereafter | Once a year |

antimicrobial agent. If there is no appreciable clearing by 48 hours, subconjunctival corticosteroid injections are given as frequently as two times a day. Therapy is continued until total corneal clearing occurs, usually within two to four weeks, but if no appreciable change is noted at the end of this time, it is assumed that irreversible endothelial damage has occurred, and active medication is slowly discontinued. Rarely, a patient will clear spontaneously after a prolonged period of time.

### GRAFT REACTIONS

In evaluation of graft successes or failures, a successful graft is defined as an optically clear graft on slit lamp examination except in the area of suture tracts. Short-term or early success is defined as a clear graft up to the time of suture removal (approximately three to four months). Long-term success is a graft that remains clear after this time.

*Graft failure*—This refers to an irreversible graft reaction, usually caused by primary or secondary physiologic failure of the corneal endothelium resulting in corneal edema or severe stromal scarring with central opacity of the donor cornea. Early graft failure occurred prior to suture removal, while a delayed graft failure occurred any time after suture removal.

*Early graft reaction*—The severity of early graft reactions varied markedly among patients. The degree of severity was classified as minimal, moderate, or severe (Fig. 4-A). A minimal reaction in a nonvascularized host shows virtually no vascular invasion of the host cornea. In vascularized hosts, neither engorgement nor proliferation of vessels occurs. Moderate reactions were either corneal or uveal, or both. In these cases, inflammation began at the donor–host interface and extended into the peripheral donor cornea. The central donor cornea remained free of inflammation. The uveal reaction seeded the central and inferior donor and host endothelium with keratic precipitates, often leading to corneal edema. Moderate reactions seldom led to graft failure. When graft failure occurred, it resulted from secondary ocular involvement (noncorneal) such as phthisis bulbi or glaucoma with wound failure. A severe reaction extended throughout the entire donor cornea with both corneal and uveal involvement. These cases demonstrated early graft failure.

*Delayed graft reaction*—Opacification of the cornea may occur at any time following the removal of sutures. Patients complained of suddenly decreased vision, pain, photophobia, and limbal hyperemia. It is important to note that the patients in this group were under their own recognizance during this period, so that the effect of the interval elapsing between onset of these reactions and the patient's re-presentation for examination and treatment proved very difficult to assess.

As in the early graft reaction, delayed graft inflammation is of corneal or uveal origin (Fig. 4-B). The typical reaction in almost every case is a combination of inflammatory infiltrate and edema which extends into the central cornea from the limbus, involving both host and donor corneas during active inflammation (early active stage, Fig.

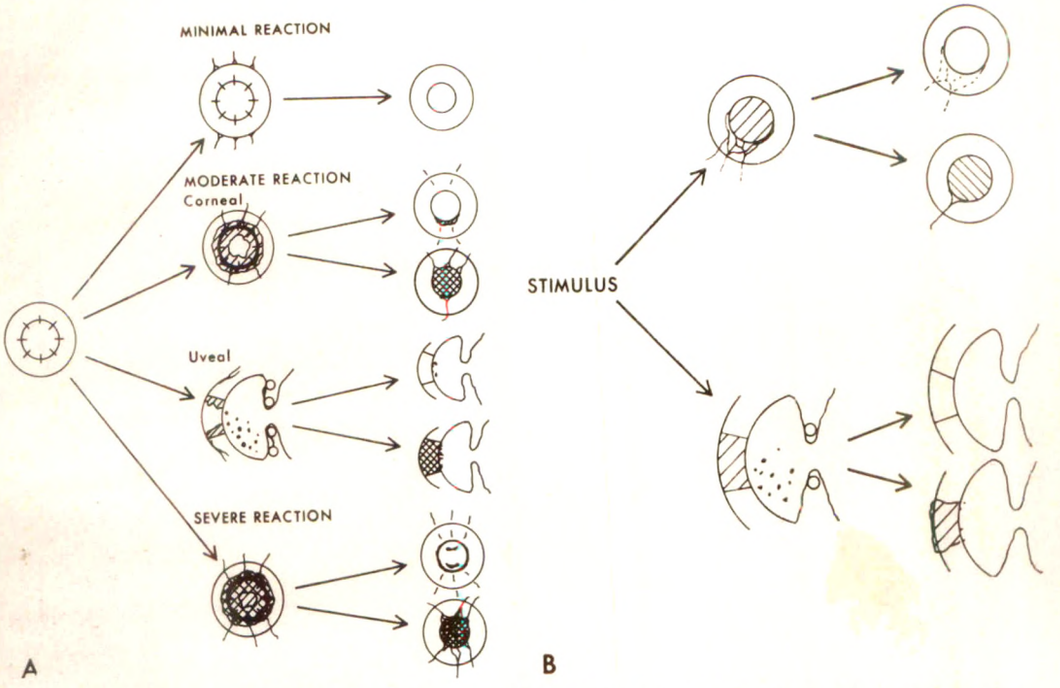



Fig. 4 (Moore and Aronson). (A) Patterns of inflammation in early graft reactions. (B) Patterns of inflammation in delayed graft reactions.

5). In inflammatory resolution, clearing of the host cornea precedes donor clearing. In delayed graft failure, the recipient cornea clears, but the donor cornea remains clouded (stage of endothelial decompensation). We have assumed that secondary physiologic failure of the donor endothelium occurs in the course of the inflammatory episode and that resultant failure is represented by bullous keratopathy.

*Evaluation of the early graft reaction*—The variables affecting the outcome in the early period include: (1) physiologic properties of the donor cornea, (2) surgical factors, (3) the effect of suture material and technique on the graft, (4) the role of conjunctival microbes, and (5) tissue noncompatibility (Fig. 6).

*Donor failure*—The clinical course of graft failure can be described accurately in many cases. Primary donor failure is characterized by non-clearing opacification of the corneal donor button from the time of surgery.[9] There is minimal corneal inflammatory response in donor or host tissue. When the donor button is replaced (usually by the 10th day) and studied histologically, there is a striking absence or degeneration of endothelial cells. Secondary epithelial and stromal edema are pronounced. The corneal stroma is surprisingly free of inflammatory cells.

*Surgical failure*—Logically, surgical failure subdivides into two types. The first results from technical error. It is manifest in some form of wound failure, compromise, or malposition of the donor–host margin. In some cases, the graft will succeed, but a large descemetocele or iris adhesion or incarceration remains at the donor–host margin, interfering with the optical quality of the graft. If donor endothelium is surgically damaged, the graft will appear as primary donor failure.

The second type is surgically induced inflammation, usually presenting as a traumatic uveitis or hyphema. Apparently, it is directly related to the extent and duration of the surgery.

*Suture toxicity reaction*—Suture toxicity

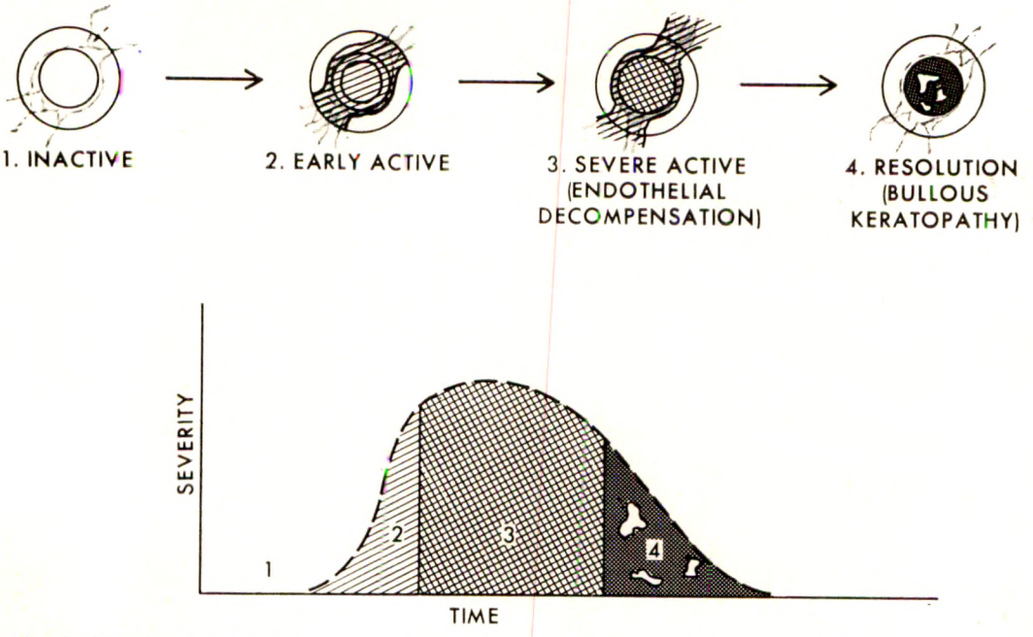



Fig. 5 (Moore and Aronson). Sequential stages in delayed graft reaction. The uveal pattern of disease proceeds through the same inflammatory stages. However, the inflammation is less severe.

presents initially as infiltrate in and around suture tracts, first in the recipient, then in the donor. This reaction gradually progresses to heavy vascularization of the suture tracts; coalescence and proliferation of these vessels can eventually culminate in neovascularization and scarring of the central donor cornea. The selection of patients and the type of suture used has been presented in Table 6, where 8-0 virgin silk (Ethicon), 9-0 virgin silk (Ethicon), and 10-0 nylon (Ethilon) sutures were compared for severity of toxic reaction. Seven cases of graft failure with silk suture were reoperated with Ethilon and appear as cases in both series.

Since graft failure decreased sharply with the advent of interrupted nylon suture, other criteria were necessary to evaluate differences in reaction between interrupted and continuous nylon suture. Such criteria were subdivided into objective and subjective classes. Objective signs of infiltrate formation and neovascularization of the suture tract are classified as absent, mild, or severe. Patients were also questioned for subjective symptoms of pain and photophobia. We must emphasize that a majority of the interrupted nylon cases (37 cases) were evaluated restrospectively so that this aspect of our study is affected by subjective interpretation.

*Microbially induced graft failure*—This commonly presents as a discrete suture abscess which is usually limited to one or two suture tracts and which may rapidly involve most of the donor cornea. If not aborted immediately, this reaction will proceed to graft failure. Pathogenic bacteria are responsible for this reaction.

Whether or not indigenous (nonpathogenic) bacteria produce a toxic reaction which may lead to graft failure is difficult to determine. The indigenous reaction is characterized by infiltrate formation and secondary vascularization around the knots of interrupted nontoxic nylon suture. When the conjunctival sac is cultured, the growth of Staphylococcus epidermidis or diphtheroids is usually prolific. When the interrupted suture is removed and epithelium allowed to close the

suture tract, the reaction disappears (Fig. 9-E and F). The continuous nylon suture allows epithelium to grow over it in a sheet free of defects; the only epithelial defect is at the suture knot when it is not placed beneath the bulbar conjunctiva (Fig. 10-G and H).

To evaluate this reaction, a series of cultures were taken from patients who had had interrupted and continuous nylon sutures. Five individuals from each group with positive cultures for indigenous bacteria were compared for the presence or absence of clinical signs described under suture toxicity.

*Tissue incompatibility reaction*—A tissue incompatibility reaction (homograft, allograft) proved exceptionally difficult to differentiate from suture or indigenous microbial reactions. Undoubtedly, this difficulty is compounded when high-dosage topical corticosteroid is used. Historically, tissue incompatibility reactions have been depicted as

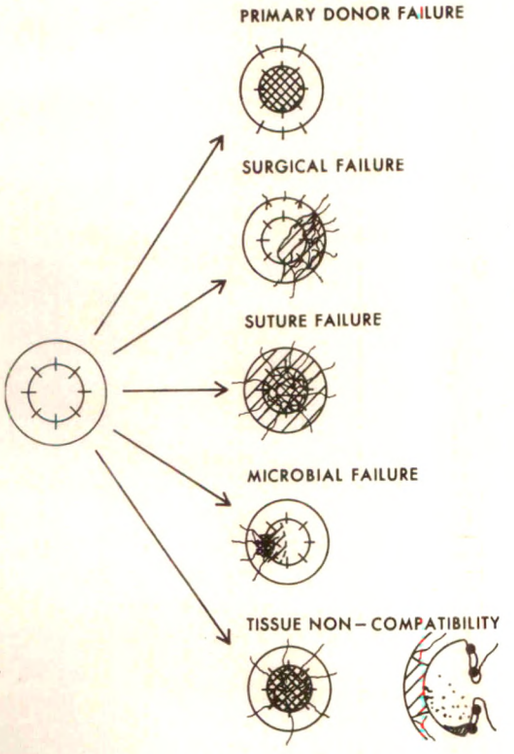



Fig. 6 (Moore and Aronson). Types of graft failure (early graft reaction).

TABLE 6

DISTRIBUTION OF SUTURE AMONG CASES

| Morphologic Class | 8-0 Silk (Interrupted) | 10-0 Ethilon (Interrupted) | 10-0 Ethilon (Continuous) |
|---|---|---|---|
| 0+ | 15 | 12 | 5 |
| 1A+ | 1 | — | — |
| 1B+ | 11 | 3 | 3 |
| 2+ | 12 | — | — |
| 3+ | 25 | 6 | 3 |
| 4+ | 31 | 30 | 6 |
| Total | 95 | 51 | 17 |

neovascularization of the donor graft or as a predominantly uveal reaction with initial rejection of donor endothelium. Although we have seen such classically described reactions, we could not differentiate tissue incompatibility from the other identifiable variables. Our experience suggests that the tissue incompatibility reaction is probably a concurrent reaction and is occasionally diagnosed by exclusion. In this series, we have been able to identify only one case as representing this mechanism.

*Late graft reaction*—The principal sources of stimuli for the delayed graft reactions have been diagrammed in Figure 7 and include: (1) surgical trauma, (2) exogenous stimuli, (3) endogenous uveitis, and (4) tissue incompatibility. (One again, this last diagnosis can only be made after excluding other potential causes.) The traumatic reaction is a consequence of direct mechanical destruction of donor endothelium, while the other three reactions are related to the acute inflammatory pathway.

The course of the delayed graft reaction may be self-limited or progressive to graft failure. There has not been an identifiable self-limited reaction within this series. Because we consider the donor endothelium to be highly susceptible to inflammation, we immediately treat such reactions with corticosteroid.

Other operative factors in the delayed graft reaction in addition to the stimulus include the

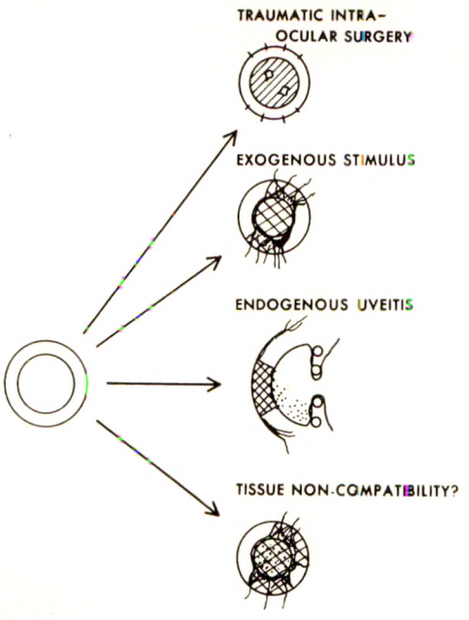



Fig. 7 (Moore and Aronson). Types of graft failure (delayed graft reaction).

immunologic characteristics of the host response, the degree of preoperative and postoperative morphologic change, and the socioeconomic status of the individual.

Stimulus evaluation for bacteria-induced inflammation was performed as described earlier. The herpes simplex virus was identified by corneal clinical morphology, culture, or electron microscopic identification. Upper respiratory virus was diagnosed by history of a concurrent or recent upper respiratory episode of disease or "flu syndrome." A diagnosis of topical allergy (epinephrine, hair spray) was based upon continued use of the allergen before the onset of corneal inflammation and disappearance of inflammation after the allergen was withdrawn. Each of the cases designated as idiopathic demonstrated some evidence of corneal vascular insufficiency[2] (two alkali keratitis, one Mooren's ulcer); however, there was no evidence of a specific stimulus. The postsurgical failure demonstrated endothelial decompensation immediately after surgery and never cleared.

Host response was evaluated by comparing the quantitative immunologic test results (Table 7) of delayed graft reaction and failure patients with those of patients without subsequent reactions.

Delayed graft reaction patients were compared by morphologic criteria both pre- and postoperatively. The preoperative classification has already been described. The postoperative classification (Fig. 11) was based upon the degree of neovascularization of the host cornea and has been divided into absent (Fig. 11-A); minimal (Fig. 11-B), in which a single arborizing branch approached the donor cornea; and moderate (Fig. 11-C and D), in which a number of vessels extended to the donor margin.

As a final variable, patients were divided into three socioeconomic groups: the private patients series; the UC clinic series, in which patients paid a reduced rate for hospital and outpatient care; and the SFGH or charity clinic series, drawn almost entirely from the indigent wards. The major differences be-

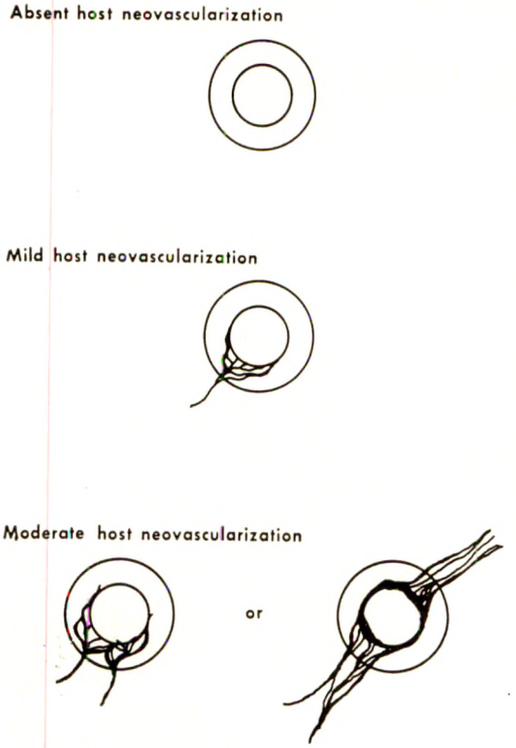



Fig. 8 (Moore and Aronson). Postoperative morphologic classification.

TABLE 7

IMMUNOLOGIC DETERMINATIONS IN DELAYED GRAFT REACTIONS

| Graft Group | Total Cases | IgA | IgM | IgG | Early IgG |
|---|---|---|---|---|---|
| Delayed reactions | 21 | 312 | 120 | 1283 | 7.7 |
| Delayed failures | 16 | 249 | 148 | 1315 | 8.2 |
| Clear grafts, no reaction | 74 | 228 | 129 | 1165 | 7.4 |

tween these groups were their family circumstances and habitus. Private and UC patients usually belonged to a functioning family unit. The SFGH patient almost always lived by himself in a boarding house, was frequently alcoholic, and was usually without regular close human contact.

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The majority of all graft failures occurred during the first 12 weeks. Of the preoperative prognostic criteria, the clinical and morphologic classification appears to be the most significant (Table 8). The case success rate dropped from 100% in 0+ recipients to 80% in 4+ recipients; 18% of cases with poor prognosis (3 and 4+) failed, compared with 5% for those with good prognosis (0, 1A, 1B, and 2+). Success rates in 1B, 3, and 4+ groups improve when analyzed by eyes and by patients. This indicates that multiple surgical procedures enhance the potential for eventual success in these groups.

Etiologic classification closely parallels the clinical and morphologic evaluation (Table 9). The good prognosis groups (e.g., keratoconus, corneal dystrophies, corneal trauma) all demonstrated 100% success. The inflammatory corneal conditions such as herpes simplex, herpes zoster, bacterial and idiopathic stromal keratitis demonstrated similar success rates. The physical and chemical keratitis group showed the poorest success rate, 77%.*

Etiologic evaluation, when grouped for eyes and patients, showed marked improvement over case results (herpes simplex, 87 vs 78%). As in the poor prognosis groups, multiple surgical procedures improved success rates. (Etiologic classification per se was not statistically evaluated since there was no comparative basis for diagnostic categories.)

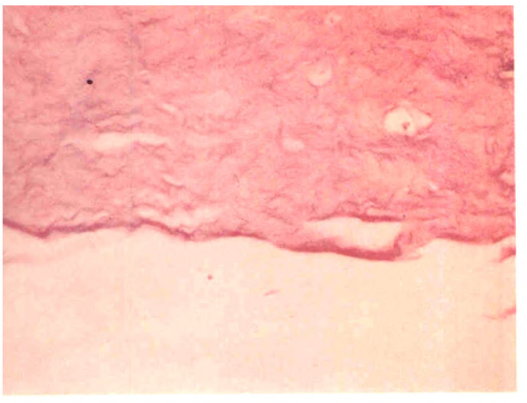
Prognosis by immunologic parameters has been evaluated by several techniques. A comparison of mean values for successful and failed cases (Table 10) revealed no significant differences ($> 2$ SD) for any testing procedure when compared with a normal population. This was true whether or not the series was differentiated by clinical–morphologic classification.

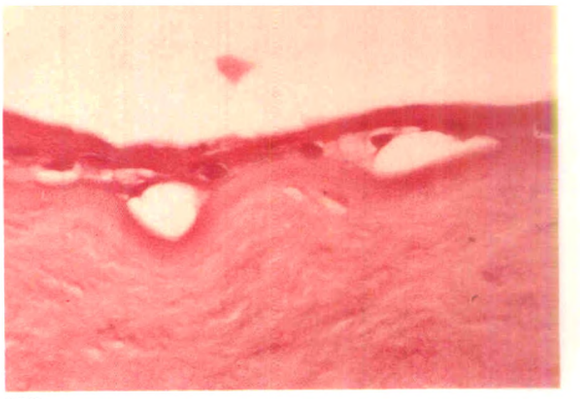
However, when a sharp cut-off distribution curve is plotted, early graft prognosis can be projected from early IgG. When the mean values for each clinical-morphologic group are plotted as the cut-off point, very few failures demonstrated early IgG values which were greater than the mean (Table 11). This has clinical usefulness for group 3 and 4+ cases, in which this early IgG distribution is the basis for selection of pre- and postoperative treatment regimens.

When the treatment administered is based on early IgG determination, the overall success rate for these cases is slightly higher than for cases treated prophylactically, providing nylon suture has been used. Because of silk suture toxicity, comparison cannot be made between the silk suture prophylactic corticosteroid group and the early IgG prognostic

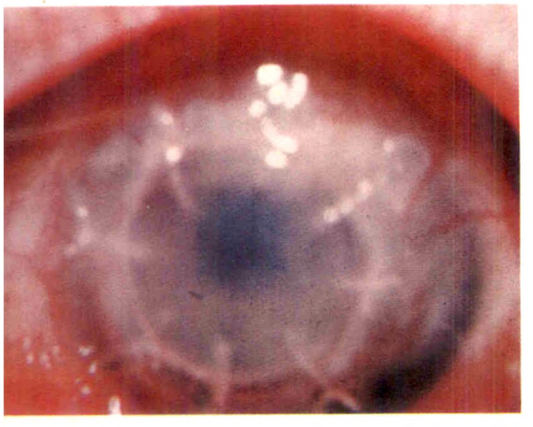
* This rate of success may improve with pre- and postoperative treatment of intravascular coagulation. Since we have used heparin in this group, four of six cases (four of five eyes and patients) have had successful grafts during the early period. This percentage is not far different from results in the other specific etiology groups.

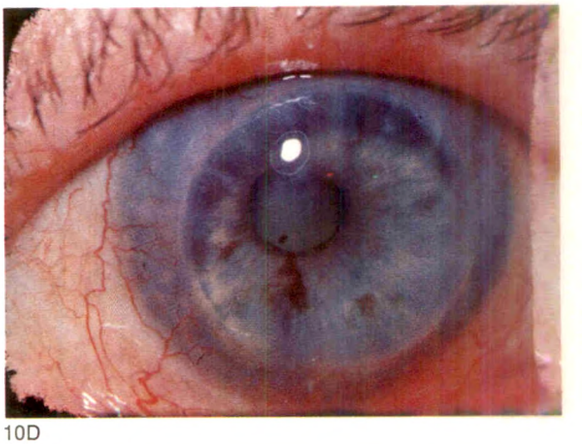
Fig. 10 (Moore and Aronson). Suture toxicity (early graft reaction). (A) Patient 6 demonstrates early failure as a result of silk suture toxicity six weeks following surgery. (B) Same patient with subsequent keratoplasty in which 10-0 Ethilon suture was used, demonstrating a clear graft 10 weeks after surgery. (C) Patient 7 demonstrates early graft failure secondary to silk suture toxicity 12 weeks after surgery. (D) same patient demonstrating a clean graft one year after surgery. 10-0 Ethilon suture was used. (E) Patient 8 at four weeks postsurgery demonstrates reaction to 8-0 silk suture, with no reaction to nylon suture. (F) Another patient with penetrating keratoplasty demonstrates reaction to 9-0 virgin silk with relative lack of reaction to nylon. (G) Another patient with keratoconus in whom continuous nylon suture was used. Suture tracts are free of infiltrate. (H) Same patient (higher magnification), demonstrating the lack of infiltrate.



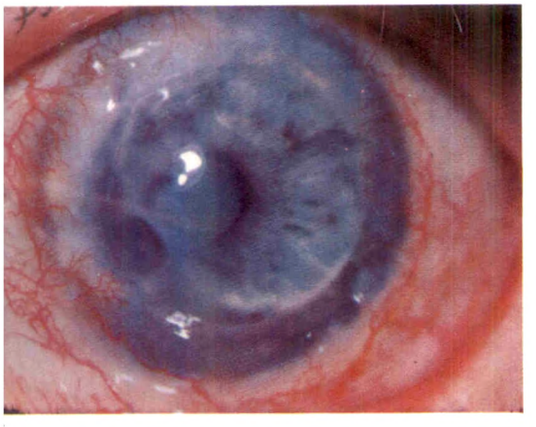


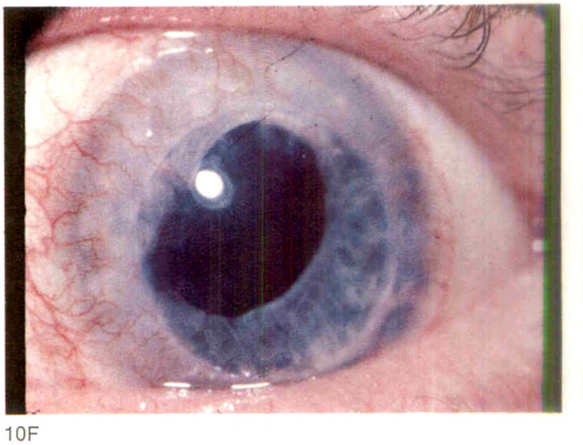
10B



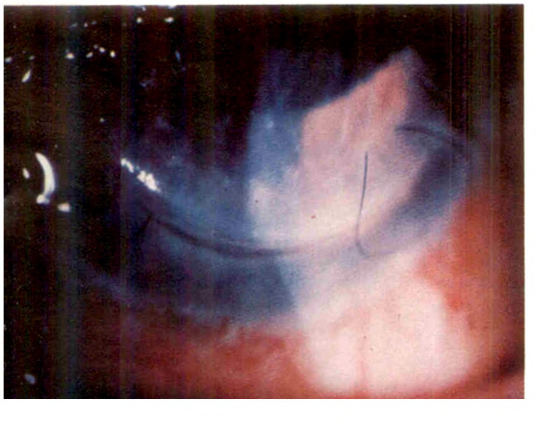


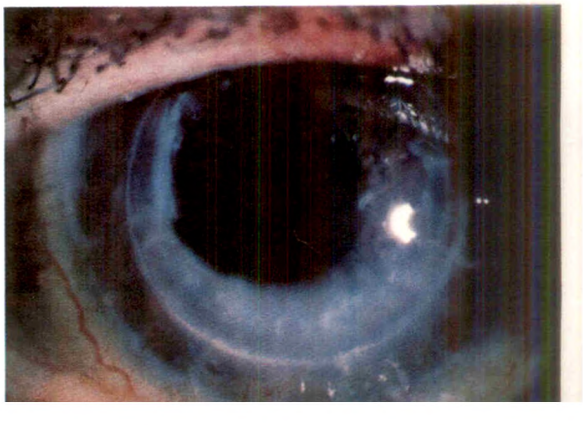
10D

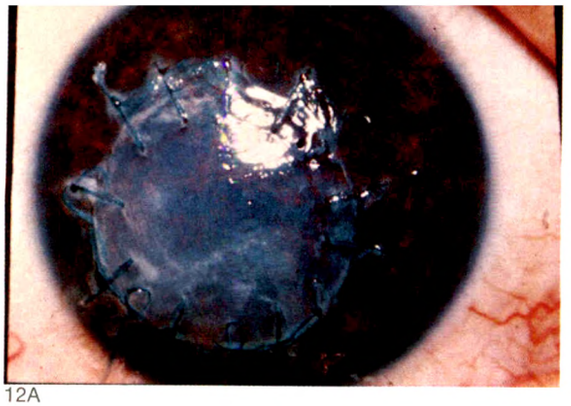




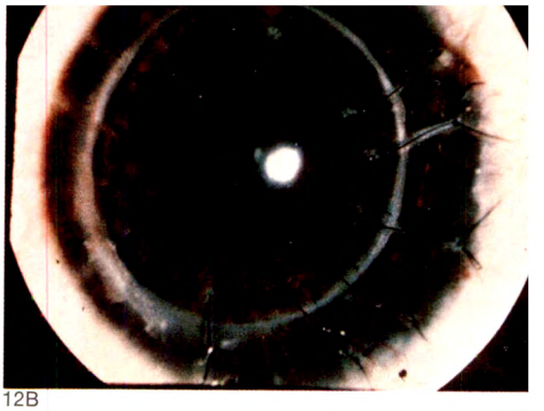
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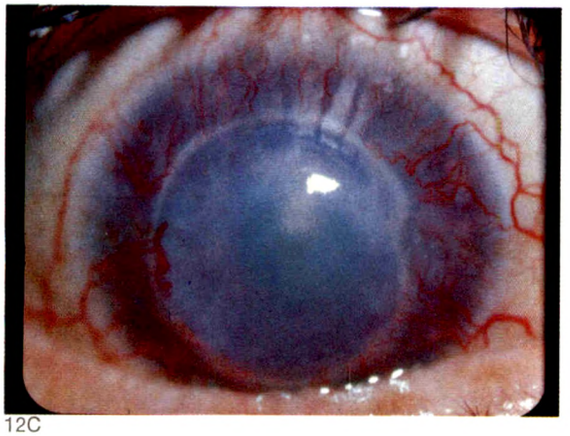




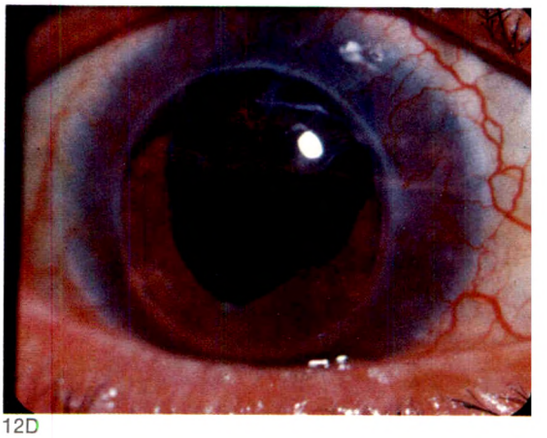
12A



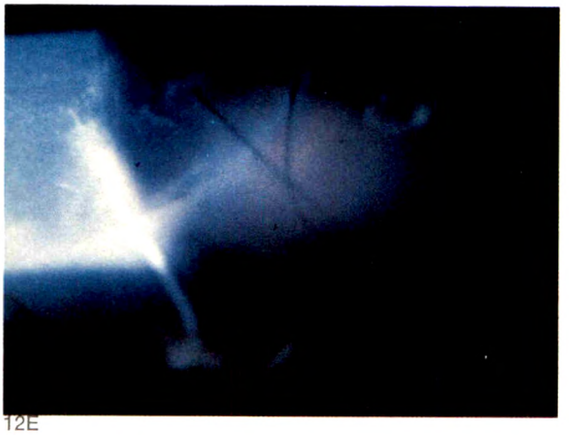
12B



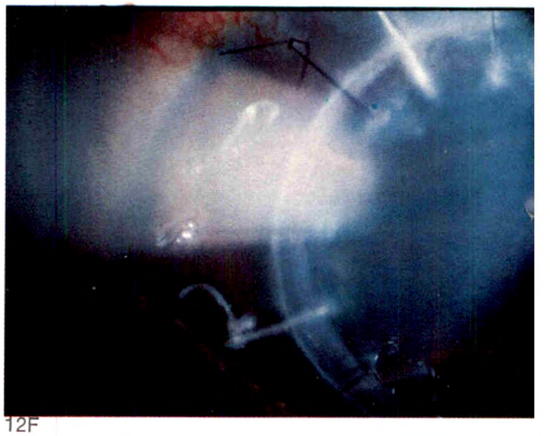
12C



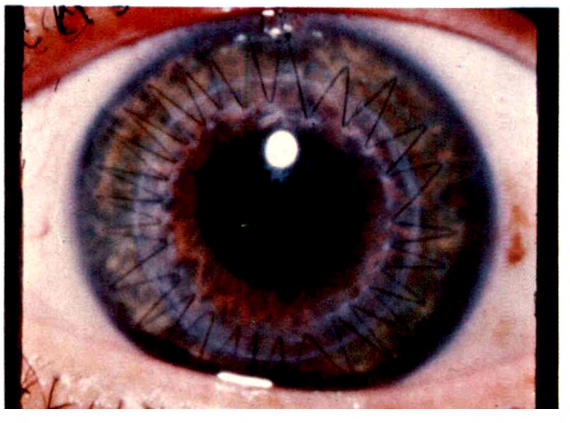
12D



12E



12F



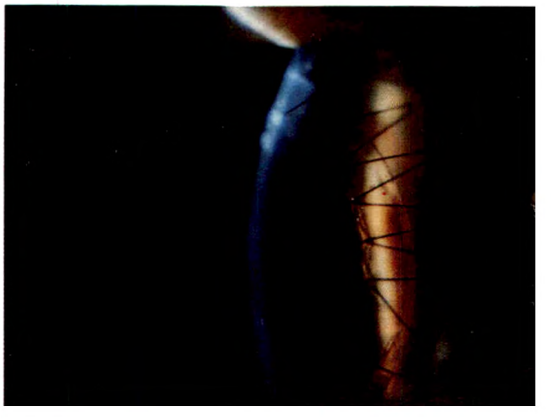


TABLE 8

SHORT-TERM (12-WEEK) KERATOPLASTY RESULTS BY MORPHOLOGIC CLASSIFICATION

| | Morphologic Classification | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 0+ | 1A+ | 1B+ | 2+ | 3+ | 4+ | |
| Total cases | 32 | 1 | 17 | 12 | 34 | 67 | 163 |
| Successful grafts | 32 | 1 | 14 | 12 | 29 | 54 | 142 |
| % successes | 100 | 100 | 82 | 100 | 85 | 81 | 87 |
| Total eyes | 32 | 1 | 11 | 12 | 31 | 57 | 144* |
| Successful grafts | 32 | 1 | 11 | 12 | 29 | 52 | 137 |
| % successes | 100 | 100 | 100 | 100 | 94 | 91 | 96 |
| Total patients | 23 | 1 | 11 | 11 | 31 | 56 | 133* |
| Successful grafts | 23 | 1 | 11 | 11 | 29 | 51 | 126 |
| % successes | 100 | 100 | 100 | 100 | 94 | 91 | 95 |

* Where more than one keratoplasty was performed, eyes and patients are designated according to most recent classification.

nylon suture groups (Table 12). This finding is particularly interesting since it demonstrates that adoption of the combined immunomorphologic criteria for selection of therapy yielded results equal to those of the routine prophylactic corticosteroid regimen.

*Evaluation of the individual variables leading to early graft failure*—Primary donor failure occurred only once in this series. Patient 1 received a 58-year-old donor's cornea 18 hours after the donor's death without deviation from our protocol. The donor cornea never cleared and by the fifth postoperative day it became apparent that the donor button was physiologically incompetent. A second penetrating keratoplasty was perpormed on the sixth postoperative day with a successful early result.

## CASE REPORT

Patient 1 was a 53-year-old Mexican American man with a history of long-standing idiopathic stromal keratitis, preoperative morphologic class 4+. A 7.5 mm penetrating keratoplasty was performed on his right eye; 16 interrupted 8-0 virgin silk sutures were used to secure the graft. The opposite eye of the donor was not used for surgery and was fixed in buffered Formalin. The graft was hazy on the second postoperative day; by the fifth day, the haziness had become more pronounced. Epithelial and stromal edema as well as folds in Descemet's membrane were present. The diagnosis of primary donor failure was made, and the patient was returned to surgery for regrafting. A second 7.5 mm donor button was placed in the right eye and secured with 16 interrupted silk sutures. The patient's postoperative course was relatively uneventful.

*Histology*—Sections of the failed donor cornea revealed stripping of endothelium from most of the posterior cornea. A large area of Descemet's membrane was missing from the temporal aspect as well (Fig. 13-A). The epithelium and stroma showed fine edematous change (Fig. 13-B). Polymorphonuclear leukocytes were noted entering the periphery of the donor cornea, indicating some degree of reaction. The control cornea (opposite eye) showed no evidence of endothelial change. We have assumed that destruction of endothelium and Descemet's membrane resulted from traumatic handling at the time of surgery.

Examples of surgically induced early graft failures are readily demonstrated. Wound failure occurred much more fre-

Fig. 12 (Moore and Aronson). Surgery-induced inflammation (early graft reaction). (A) Patient 5, preoperatively demonstrates a large central descemetocele below a partially retracted flap. (B) Postoperative endophthalmitis (photograph taken eight weeks following surgery). (C) Histology of ciliary body demonstrates a low-grade cyclitis. (D) Histology of posterior eye shows perivascular cellular cuffing of a retinal vessel with minimal-to-absent vitreous involvement.

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TABLE 9

SHORT-TERM (12-WEEK) KERATOPLASTY RESULTS BY ETIOLOGIC CLASSIFICATION

| | Total Cases | Successful Grafts | | Total Eyes | Successful Grafts | | Total Patients | Successful Grafts | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | | No. | % | | No. | % |
| Keratoconus | 14 | 14 | 100 | 14 | 14 | 100 | 12 | 12 | 100 |
| Corneal dystrophy | 17 | 17 | 100 | 17 | 17 | 100 | 10 | 10 | 100 |
| Aphakic bullous keratopathy | 30 | 27 | 90 | 27 | 27 | 100 | 27 | 27 | 100 |
| Trauma | 6 | 6 | 100 | 6 | 6 | 100 | 6 | 6 | 100 |
| Herpes simplex | 37 | 29 | 78 | 31 | 27 | 87 | 31 | 27 | 87 |
| Herpes zoster | 5 | 5 | 100 | 5 | 5 | 100 | 5 | 5 | 100 |
| Bacterial keratitis | 7 | 6 | 86 | 6 | 6 | 100 | 6 | 6 | 100 |
| Idiopathic stromal keratitis | 26 | 21 | 81 | 21 | 19 | 90 | 20 | 18 | 90 |
| Physical or chemical agent | 13 | 10 | 77 | 10 | 9 | 90 | 10 | 9 | 90 |
| Other diagnoses | 8 | 7 | 87 | 7 | 7 | 100 | 6 | 6 | 100 |
| Total | 163 | 142 | 87 | 144 | 137 | 95 | 133 | 126 | 95 |

quently when silk suture was used (Table 13). It presented as a separation of the donor and recipient cornea with suture erosion of either area. The disappearance of this complication with the advent of nylon suture is most readily explained by this suture's elasticity and plasticity. Swelling of either donor or host tissue no longer produced suture tract erosion.

Patient 2 demonstrates a wound dehiscence involving silk suture. The poor quality of the temporal aspect of the host cornea made suturing extremely difficult. On the fourth postoperative day, the margin of the

TABLE 10

IMMUNOLOGIC DETERMINATIONS IN KERATOPLASTY

| Diagnostic Category | | Total Cases | Immunologic Determinations | | | |
|---|---|---|---|---|---|---|
| | | | IgA | IgM | IgG | Early IgG |
| 0+ | Success | 25 | 259 | 101 | 1112 | 6.9 |
| | Failure | | | | | |
| 1A+ | Success | 1 | 301 | 28 | 1032 | 7.5 |
| | Failure | | | | | |
| 1B+ | Success | 12 | 214 | 153 | 1111 | 7.1 |
| | Failure | 3 | 299 | 96 | 1227 | 7.4 |
| 2+ | Success | 11 | 270 | 87 | 1034 | 7.5 |
| | Failure | | | | | |
| 3+ | Success | 25 | 256 | 120 | 1200 | 7.4 |
| | Failure | 6 | 315 | 88 | 1031 | 6.6 |
| 4+ | Success | 50 | 241 | 150 | 1300 | 7.8 |
| | Failure | 12 | 173 | 125 | 1075 | 6.1 |
| Total | Success | 126 | 247 | 130 | 1204 | 7.7 |
| | Failure | 21 | 232 | 110 | 1084 | 6.4 |

TABLE 11

EARLY IgG IN GRAFT RESULTS

| Category | Outcome | Silk Suture | All Sutures |
|---|---|---|---|
| 0+ | Success | 6.5 | 6.9 |
| | Failure | | |
| 1A+ | Success | 7.5 | |
| | Failure | | |
| 1B+ | Success | 7.0 | 7.1 |
| | Failure | 7.4 | 7.4 |
| 2+ | Success | 7.5 | 7.5 |
| | Failure | | |
| 3+ | Success | 8.0 | 7.4 |
| | Failure | 6.7 | 6.5 |
| 4+ | Success | 9.2 | 8.1 |
| | Failure | 6.6 | 6.3 |
| Total | Success | 7.8 | 7.7 |
| | Failure | 6.8 | 6.4 |

donor cornea swelled and pulled three silk sutures out of host tissue. An iris prolapse resulted. After the cornea was resutured, a severe graft reaction occurred and the graft went on to failure (Fig. 13-C).

### CASE REPORT

Patient 2 was a 62-year-old Caucasian man, alcoholic and unemployed, with a history of idiopathic stromal keratitis and failed lamellar keratoplasty, preoperative morphologic class 3+. The patient was regrafted with a 7.5 mm penetrating graft sutured with 16 interrupted virgin silk sutures. At surgery it was noted that the cornea was extremely thin temporally, therefore, long recipient suture bites were placed. The patient was started on protocol postoperative medication. By the fifth postoperative day, a marked swelling of the donor cornea was noted temporally. By the eighth day, three sutures had pulled out of the recipient cornea and a frank wound dehiscence presented. The donor cornea was braced with a Werb splint, which was kept in position for three weeks and removed after the wound had healed sufficiently. By this time, irreversible donor infiltrate and neovascularization had occurred (Fig. 13-C). The patient was regrafted successfully with a 7.5 mm penetrating keratoplasty (Fig. 13-D). Following cataract extraction, the patient's visual acuity was correctable to 20/20 with a contact lens.

TABLE 12

RESULTS OF PROPHYLACTIC VS SELECTED CORTICOSTEROID THERAPY

| | Total Cases | Successful Grafts | |
|---|---|---|---|
| | | No. | % |
| Corticosteroid prophylaxis | | | |
| Silk suture | 95 | 77 | 81 |
| Nylon suture | 22 | 20 | 91 |
| Corticosteroid on indications | | | |
| Nylon suture | 46 | 45 | 98 |

A more frequent form of wound dehiscence or slippage occurs following suture removal. Such an example occurred in case 3, when silk sutures were removed eight weeks following surgery. The resultant inferonasal descemetocele was so large (Fig. 13-E) that a contact lens was contraindicated and spectacle correction was 20/200.

### CASE REPORT

Patient 3 was a 52-year-old Caucasian man with a long history of alkali keratitis. There was no evidence of intraocular disease, so preoperative morphologic classification was 3+.

TABLE 13

COMPLICATIONS OCCURRING IN THE EARLY GRAFT PERIOD

| Type of Complication | Silk Suture | | | Nylon Suture | | |
|---|---|---|---|---|---|---|
| | Total Cases | Complication | | Total Cases | Complication | |
| | | No. | % | | No. | % |
| Early wound dehiscence | 95 | 10 | 11 | 68 | 2 | 3 |
| Late wound slippage | 95 | 2 | 2 | 68 | 4 | 6 |
| Total | 95 | 12 | 13 | 68 | 6 | 9 |

An 8.0 mm penetrating keratoplasty was performed and sutured with 16 interrupted 8-0 virgin silk sutures. The patient's postoperative course was relatively uneventful. However, when suture removal was begun (eight weeks postoperatively), a wound separation appeared in the eight o'clock meridian. Remaining sutures were left in position and the eye was double-patched. A large descemetocele formed between seven and nine o'clock (Fig. 13-E). Because of this large wound defect and the unsatisfactory visual result, the patient was regrafted and a cataract extraction was performed with a successful result (Fig. 13-F).

There was no significant difference between silk and nylon suture cases in the incidence of late wound slippage (Table 13). However, nylon suture considerably prolongs wound healing; if it is allowed to remain in position for an adequate period of time, late wound slippage can be avoided. It is important to note that silk sutures were removed at approximately 12 weeks and nylon sutures between 16 to 18 weeks following surgery.

An unusual type of early wound failure was encountered in one case sutured with nylon. In patient 4, a continuous nylon suture was cut unintentionally during removal of an anchoring suture three weeks postoperatively. As the suture retracted, a large inferior wound dehiscence resulted, which required resuturing (Fig. 13-G). The remaining postoperative course was uneventful with a resultant clear donor cornea (Fig. 13-H).

### Case report

Patient 4 was a 70-year-old Caucasian woman with Fuchs' corneal dystrophy, morphologic classification 0+. The right eye had been operated upon one year previously, with an excellent corneal result. However, fundus examination revealed a discrete macular hole. A 7.5 mm penetrating keratoplasty was performed on the left eye. The button was anchored with four interrupted nylon sutures followed by a continuous nylon suture. On the second postoperative day, an intumescent lens developed with consequent pupillary block, and by the sixth postoperative day, intractable glaucoma developed. A peripheral iridectomy was performed. The intraocular pressure was not satisfactorily controlled. On the eighth postoperative day, an intracapsular lens extraction was performed with glaucoma control subsequently achieved.

The patient's further course was uneventful. However, on the 21st postoperative day, the nylon stay sutures were removed, and while the six o'clock suture was being removed, the continuous nylon suture was unintentionally cut. The continuous suture unraveled, the wound dehisced and was plugged by iris (Fig. 13-G). The patient was taken to surgery, where the ends of the continuous sutures were tied inferiorly (with a resultant anterior synechia). The remainder of her postoperative course was uneventful. Five months postoperatively, the sutures had been removed (Fig. 13-H) and her visual acuity was correctable to better than 20/50.

The overall effect of surgical trauma and its relationship to graft failure is difficult to evaluate. The culmination of such trauma is glaucoma or hypotony which may be preceded by severe uveitis or endophthalmitis. In either case, the success of the graft is dependent upon normalization of ocular pressure. The postoperative uveitis may directly destroy the graft by destroying donor endothelial cells. Case 5 developed a progressive endophthalmitis during the fifth postoperative week which eventually led to phthisis bulbi and consequent graft failure. This blind, painful eye was enucleated after 14 weeks (Fig. 12-B).

### Case report

Patient 5 was a 65-year-old Caucasian woman referred because of a perforated right cornea secondary to a 25-year history of herpes simplex keratitis over which a bridge flap had been pulled and had retracted (Fig. 12-A). A penetrating 8.0 mm keratoplasty was performed and sutured with 16 interrupted 8-0 virgin silk sutures. In spite of continuous topical corticosteroid and IUDR therapy, this keratoplasty resulted in graft failure, probably attributable to silk suture toxicity.

After one year, the patient's failed graft was reoperated, morphologic classification 4+. This time, an 8.0 mm penetrating keratoplasty was performed using 16 interrupted Ethilon sutures. During the first postoperative week, the patient developed a hypopyon which rapidly cleared following topical and subconjunctival corticosteroid therapy. Her postoperative course was uneventful until the sixth week, by which time topical corticosteroid and IUDR had been tapered to four times a day. She then developed a relatively severe iridocyclitis. Corticosteroid therapy and IUDR were increased to hourly drops, and subconjunctival injections were resumed three times a week. Although her cornea remained clear during this period (four weeks), the anterior chamber and vitreous reaction were relatively constant and the graft clouded (Fig. 12-B). Intraocular pressure decreased until by the end of the 10th

week the eye became phthisical. The patient now requested enucleation, and her eye was removed in the 14th postoperative week.

The classification of this inflammation as secondary to surgical trauma is difficult to justify because of the long hiatus after surgery. Two other alternatives provide possible explanations for this delayed intraocular inflammation: (1) an intraocular herpes simplex infection, or (2) intravascular clotting secondary to corticosteroid therapy. Selected uveal sections were scrutinized extensively by electron microscopy, but no trace of herpes simplex virus was found. Histologic evaluation of uveal vasculature showed no active evidence of intravascular clotting. The inflammatory reaction had subsided markedly and was now present only in the anterior eye (Fig. 12-C and D). The choroid and retina were relatively free of inflammation.

The composite of individual surgical complications reflects the reproducibility of the surgery. Evaluation of early success rates (12 weeks) through successive chronologic intervals roughly indicates the overall proficiency of the surgical group (Table 14). There is a marked improvement throughout the course of the first three time periods, from 75 to 85 to 96% success. An analysis of this improvement suggests that the change from 75 to 85% success probably represents refinements in surgical technique and postoperative management; the subsequent improvement to 96% must be attributed to the adoption of nylon suture. Whether surgical improvement was also a factor in this increased success cannot be determined. Of particular interest is an evaluation of the rates of success achieved by the staff surgeon compared to that of the residents in this series. (As noted earlier, the surgical procedure was standardized by the supervision of the staff surgeon, T.E.M., Jr., in every case.) Early graft results were similar for each group (Table 15).

A second evaluation was the influence of surgical trauma, as expressed by the type of surgical procedure, upon graft outcome (Table 16). As already noted, three different surgical groups were evaluated. Although the agonal period (first several weeks after surgery) showed a greater complication rate in combined procedures, the overall results at the end of the early period did not differ significantly for all groups. Therefore, extent of intraocular surgery does not necessarily affect the outcome of the graft. However, the incidence of reduced vision from secondary complications is somewhat higher in the more complicated surgical cases (Table 17).

TABLE 14

CHRONOLOGIC EVALUATION OF SURGICAL RESULTS

| Chronologic Period | Total Cases | Clear Grafts | |
|---|---|---|---|
| | | No. | % |
| 8-0 Virgin silk | | | |
| 1965–67 | 36 | 27 | 75 |
| 1967–68 | 59 | 50 | 85 |
| 10-0 Ethilon | | | |
| 1968–69 | 51 | 49 | 96 |
| 1969– | 17 | 16 | 94 |
| Total | 163 | 142 | 87 |

TABLE 15

COMPARISON BETWEEN PRIVATE AND STAFF SURGERY CASES
(Early graft period)

| Patient Series | Total Cases | Prognosis | | Graft Success | |
|---|---|---|---|---|---|
| | | Good | Poor | No. | % |
| Private | 101 | 31 | 70 | 85 | 84 |
| UC | 38 | 26 | 12 | 35 | 92 |
| SFGH | 24 | 5 | 19 | 22 | 92 |
| Total | 163 | 62 | 101 | 142 | 87 |

TABLE 16

EFFECT OF SURGICAL PROCEDURE ON GRAFT RESULTS DURING EARLY GRAFT PERIOD

| Surgical Group | Total Cases | Early Success | |
|---|---|---|---|
| | | No. | % |
| PK* | 127 | 111 | 87 |
| PK+cataract | 18 | 17 | 94 |
| PK+anterior chamber revision | 18 | 14 | 78 |
| Total | 163 | 142 | 87 |

* PK = penetrating keratoplasty.

TABLE 17

EFFECT OF SURGICAL PROCEDURE ON NONCORNEAL OCULAR COMPLICATIONS DURING EARLY GRAFT PERIOD

| | Surgical Group | | | Total |
|---|---|---|---|---|
| | PK* | PK and Cataract Extraction | PK and Anterior Chamber Revision | |
| Total cases | 128 | 18 | 18 | 163 |
| Visual acuity >20/40 | 72 (56%) | 13 (61%) | 5 (28%) | 90 (55%) |
| Related variables: | | | | |
| Wound dehiscence | 14 | 1 | 1 | 16 |
| Glaucoma | 24 | 9 | 9 | 41 |
| Retinal detachment | 6 | 1 | 2 | 9 |
| Other | 4 | 1 | 8 | 12 |
| Total | 48 | 12 | 20 (78%) | 80 |
| Nonrelated variables | 42 | 4 | 8 | 54 |

* PK = penetrating keratoplasty.

The complication rate, 78%, was much higher in the penetrating keratoplasty plus anterior segment revision than in the other procedures. This difference apparently reflects a combination of the preoperative condition of the eye and the effect of a complicated surgical procedure. The relationship of the different surgical procedures to long-term effects appears to be much the same as the 12-week results (Table 18). Most of the complications which related to the type of surgical procedure occurred in the early graft period In summary, the extensiveness of the surgical procedure has had negligible effect on graft outcome but is related to the overall visual result of the operated eye.

The role of suture toxicity in graft success proved to be a crucial variable. The occurrence of wound dehiscence was considerably diminished when routine use of nylon suture was adopted (Table 13). Silk suture toxicity occurs as a progressive inflammatory reaction extending into the donor suture tracts and, eventually, into the central donor cornea with graft failure. Case 6 demonstrated a severe reaction to silk suture which culminated in graft failure (Fig. 10-A). He was subsequently operated with nylon suture and had an uneventful course (Fig. 10-B).

CASE REPORT

Patient 6 was an eight-year-old Mexican boy who presented with unilateral herpetic stromal keratitis, morphologic classification 3+. His right eye had previously been operated upon with a lamellar keratoplasty which became opaque. A 7.5 mm penetrating keratoplasty was performed, sutured into position with 12 virgin silk 8-0 sutures. Despite heavy corticosteroid coverage, the suture tracts demonstrated neovascularization, coalescence of these new vessels, progressive graft opacity, and, finally, graft failure (Fig. 10-A). The patient was operated upon 18 months after the original proce-

TABLE 18

CONCOMITANT OCULAR DISEASES SEEN DURING LONG-TERM FOLLOW-UP PERIOD

| Condition | Total Eyes | Eyes with Complications | |
|---|---|---|---|
| | | No. | % |
| | 129* | 47 | 37 |
| Glaucoma | | 17 | 13 |
| Cataract | | 7 | 5+ |
| Retinal detachment | | 6 | 5 |
| Senile macular degeneration | | 6 | 5 |
| Optic atrophy | | 4 | 3 |
| Amblyopia ex anopsia | | 4 | 3 |
| Enucleation or phthisis bulbi | | 5 | 4 |
| Anterior chamber membrane | | 3 | 2+ |
| Keratitis sicca | | 2 | 1 |
| Pseudopterygium | | 2 | 1 |

* Some patients died or were lost to follow-up.

dure; this time, an 8.0 mm donor button was sutured in position with 16 interrupted 10-0 Ethilon sutures. (The corneal button was negative for herpes virus on culture and electron microscopy.) The postoperative period was relatively uneventful; corticosteroids were discontinued by the sixth postoperative week (Fig. 10-B). Sutures were removed 12 weeks postoperatively. The patient demonstrated visual acuity of >20/25 over 15 months following surgery.

Patient 7 also demonstrated silk suture toxicity with consequent graft failure (Fig. 10-C). A successful result was achieved in a subsequent keratoplasty with nylon suture (Fig. 10-D).

### Case report

Patient 7 was a 49-year-old Mexican man with a long-standing history of herpes simplex stromal keratitis, morphologic classification 4+. A penetrating 7.5 mm graft was sutured with 12 interrupted 8-0 virgin silk sutures. Suture tracts rapidly vascularized; however, the central cornea remained clear through the sixth postoperative week. At this point, a surge of vessels invaded the temporal graft which could not be controlled by subconjunctival corticosteroid therapy. The graft became opaque and eventually failed. The patient demonstrated epithelial bullae with sporadic epithelial breakdown; one such occasion resulted in superinfection with pneumococcus and subsequent severe opacity and vascularization (Fig. 10-C).

The patient was re-operated upon 11 months later, at which time an 8.0 mm penetrating keratoplasty was sutured into position with 16 interrupted 10-0 Ethilon sutures. The postoperative course was quiet, although the patient has required maintenance corticosteroid and IUDR (1 drop once a day). The graft has been clear for over one year (Fig. 10-D), with visual acuity greater than 20/25 (contact lens).

In another patient (patient 8), 8-0 silk and 10-0 nylon sutures were alternately interrupted in a penetrating graft. The difference in degree of reaction rapidly became apparent (Fig. 10-E) and the silk sutures had to be removed.

### Case report

Patient 8 was a 13-year-old Negro boy with bilateral keratoconus, morphologic classification 0+. The left eye had been operated upon one year ago using 8-0 virgin silk with a successful result. Because of this, it was decided to alternate 8-0 virgin silk and 10-0 Ethilon sutures in the right eye so that a comparison could be made concerning the degree of toxic inflammogenesis. By the fourth postoperative week, the silk suture tracts showed severe infiltrate formation with some evidence of neovascularization, while the nylon sutures were relatively free of infiltrate in suture tracts (Fig. 10-E). Silk sutures were subsequently removed, the patient progressing to a successful keratoplasty.

TABLE 19

Comparison of results with several sutures
(Early graft reaction)

| Suture Group | Total Cases | Clear Grafts | % Success |
|---|---|---|---|
| All cases | 163 | 142 | 87 |
| Silk suture | 95 | 77 | 81 |
| Ethilon suture | 68 | 65 | >95 |
| Poorer prognosis | | | |
| Cases | 99 | 81 | 82 |
| Silk suture | 55 | 40 | 73 |
| Ethilon suture | 44 | 41 | 93 |
| Better prognosis | | | |
| Cases | 64 | 61 | 95 |
| Silk suture | 40 | 37 | 92 |
| Nylon suture | 24 | 24 | 100 |

A similar comparison between 9-0 virgin silk and 10-0 nylon was made in a keratoconus case. The silk suture showed an enhanced degree of infiltrate formation in suture tracts (Fig. 10-F).

When continuous nylon suture is used in a cornea with good prognosis, clinical inflammogenesis is no longer recognizable. This was demonstrated in a keratoconus case in which the suture tract, eight weeks postoperatively, was absolutely free of infiltrate (Fig. 10-G and H). Therapy was limited to maintenance corticosteroid (once a day).

Overall evaluation of suture effect reveals a marked increase in early graft success when nylon suture is used (Table 19): The rate of success is now > 95% compared to a previous 81%. A comparison of cases with poor prognosis emphasizes the significance of this difference in success. Ninety-three percent of nylon suture-treated patients demonstrated successful keratoplasties, while silk suture success fell to 73%. Naturally, cases with better prognosis showed a less significant difference, 100 vs 92%. It seems likely that the more reactive, vascular-

ized host cornea (3 and 4+) responded more vigorously to silk suture than the less reactive group with the better prognosis. On a less significant level, this difference in suture toxicity has been demonstrated in seven eyes, each of which had experienced one or more graft failures with silk suture and which succeeded when nylon suture was used.

Evaluation of the exogenous environment in relation to graft results concentrated on conjunctival microbes. Pathogenic bacterial reactions present as a suture abscess, which, if not immediately and actively treated, will progress to destroy the graft. Patient 9 incurred pseudomonas infection following surgery. However, corticosteroid and polymyxin B therapy was instituted rapidly, and the central donor cornea was kept free of inflammation (Fig. 9).

### Case report

Patient 9 was a 53-year-old Caucasian woman. She had a resolved pseudomonas corneal ulcer (Fig. 9-B), morphologic classification 4+. Before keratoplasty she was transferred to the pulmonary therapy service to increase her vital capacity for general anesthesia. During this period (approximately three weeks), ocular medication was discontinued.

When she returned to the eye service, she was inadvertantly taken to surgery without being recultured for pseudomonas. An 8.0 mm penetrating keratoplasty with partial iris excision was performed. The donor cornea was secured with 16 interrupted 8-0 virgin silk sutures. Postoperative medication, started two days after surgery, included hourly polymyxin B and topical corticosteroid four times daily. By the fourth postoperative day, a suture abscess was diagnosed in both recipient and donor corneas in the eight o'clock meridian (Fig. 9-C). Conjunctival cultures were taken, serum drawn for immunologic evaluation, and the patient immediately started on twice daily subconjunctival corticosteroid injection as well as hourly Polysporin drops. Pseudomonas was identified on culture, and IgM deficiency (80 mg/100 ml) noted on immune globulin determination. The area of suture abscess rapidly contracted so that by the ninth postoperative day it was limited to the suture tract. Cultures were negative at this time. Therapy was decreased to hourly corticosteroid drops and Polysporin four times a day. The patient demonstrated an uneventful course thereafter. Following suture removal, she demonstrated a clear graft (Fig. 9-D).

TABLE 20

INCIDENCE OF PATHOGENIC MICROBIAL DISEASE IN EARLY GRAFT PERIOD

| Entity | Cases | Successful Results | |
|---|---|---|---|
| | | No. | % |
| Bacterial | 4 | 4 | 100 |
| Viral | 2 | 0 | 0 |
| Total* | 6 | 4 | 67 |

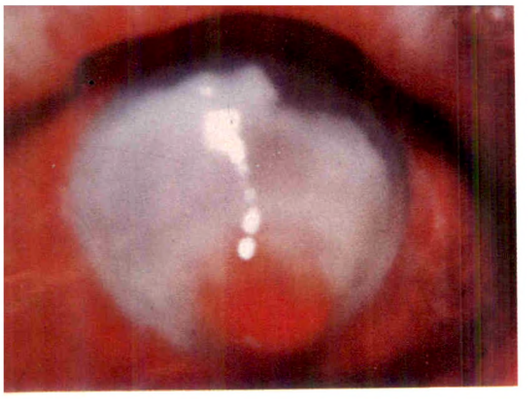
* Of 163 patients, six demonstrated pathogenic microbial involvement, an incidence of <37%.

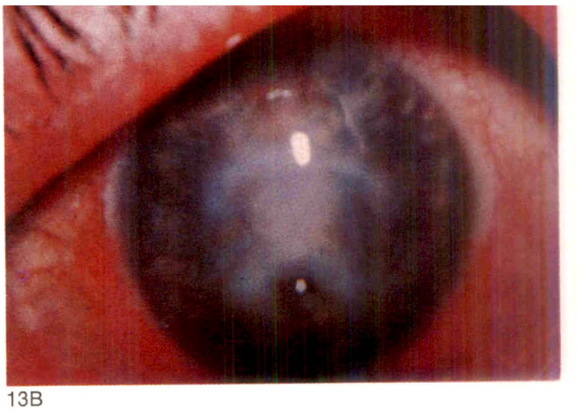
Viral infections were more difficult to diagnose during the early period. In two graft patients, a recurrent herpes simplex infection was demonstrated by electron microscopy in the donor graft during the early graft period. Both cases had progressed to early graft failure. In all, we have identified six microbial infections during the early graft period (Table 20). All bacterial cases were successfully treated, while known viral cases went on to graft failure.

The role of nonpathogenic indigenous microbes was evaluated because of the continued

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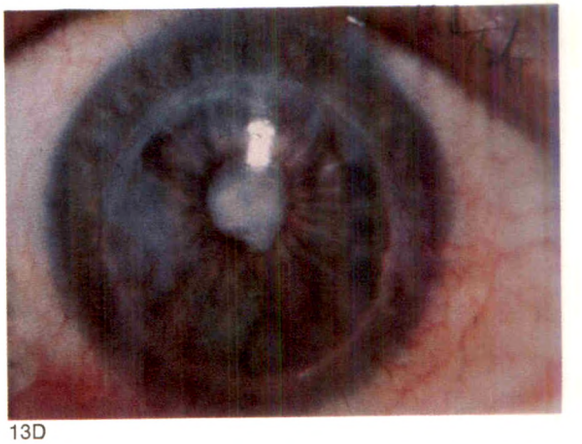
Fig. 13 (Moore and Aronson). A–B. Primary donor failure (early graft reaction). (A) Patient 1, histology of donor cornea demonstrating endothelial stripping (×40). (B) Same patient, demonstrating sub- and intraepithelial edema. C–H. Surgery-induced early graft reactions. (C) Patient 2, graft failure following wound dehiscence, pictured 10 weeks after surgery. (D) Same patient four months after subsequent keratoplasty. (E) Patient 3, descemetocele following wound dehiscence at the time of suture removal. (F) Same patient, demonstrating a subsequently clear graft six months postoperatively. (G) Patient 4, demonstrating wound dehiscence following cutting of the continuous nylon suture (three weeks postoperation). (H) Same patient at six months after surgery with a clear graft. Note the area of inferior scarring.



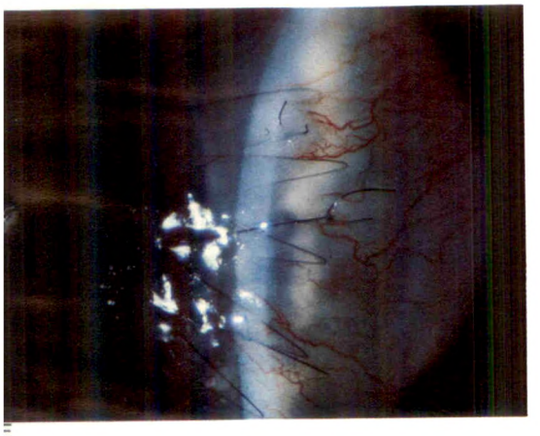


13B



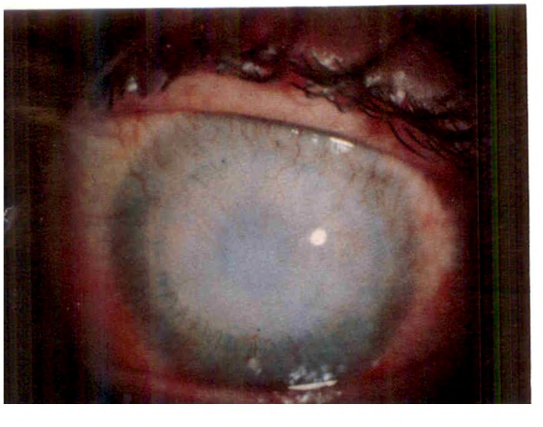


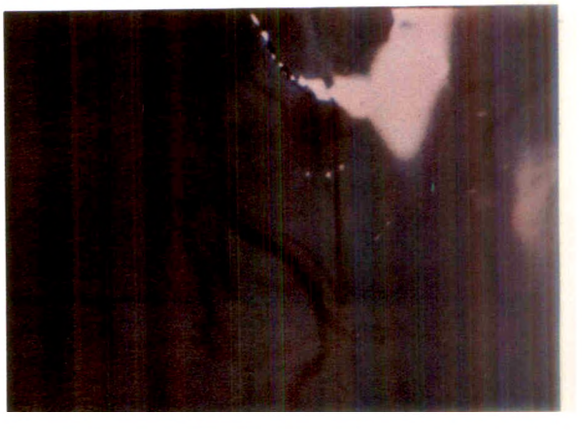
13D

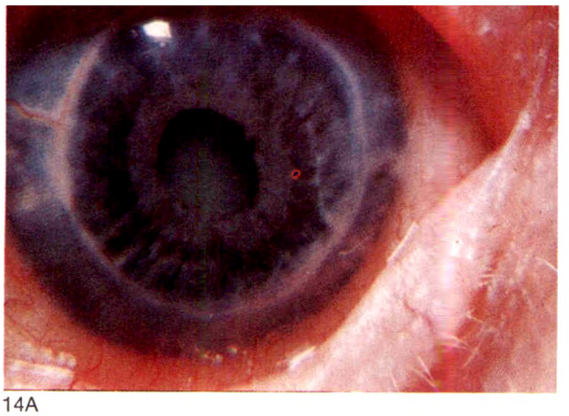




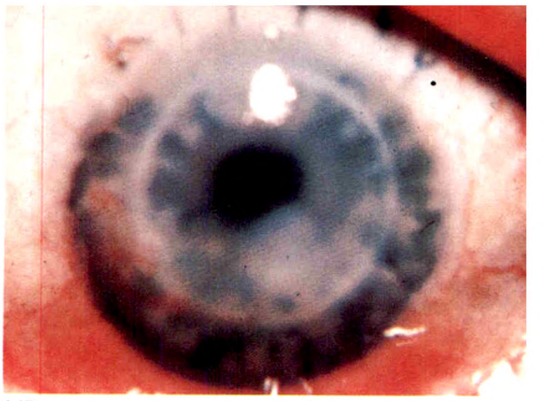
13F



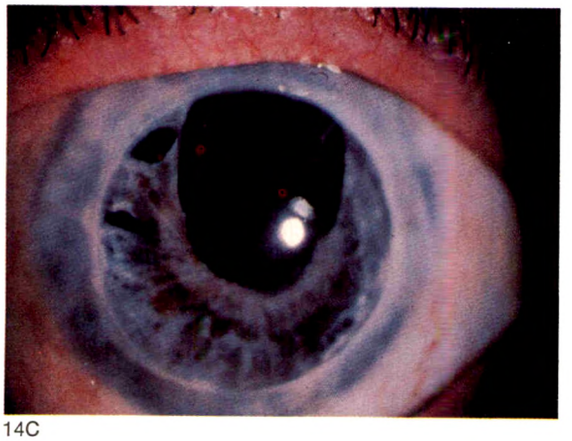




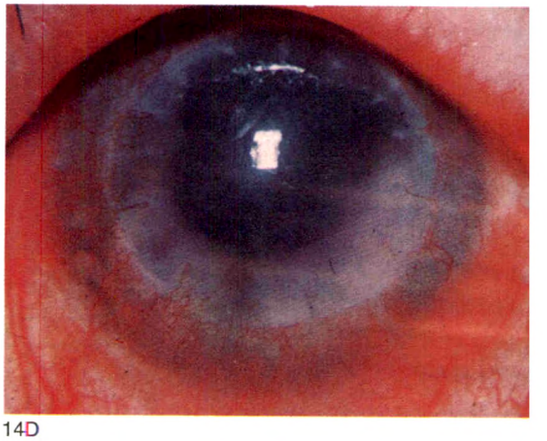
14A



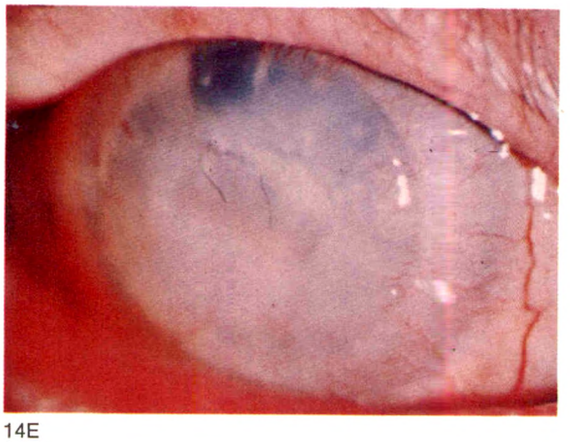
14B



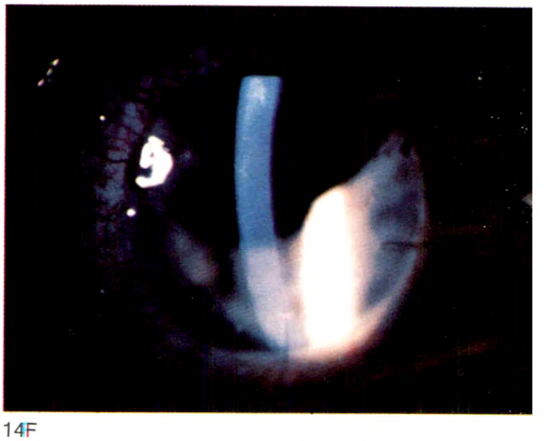
14C



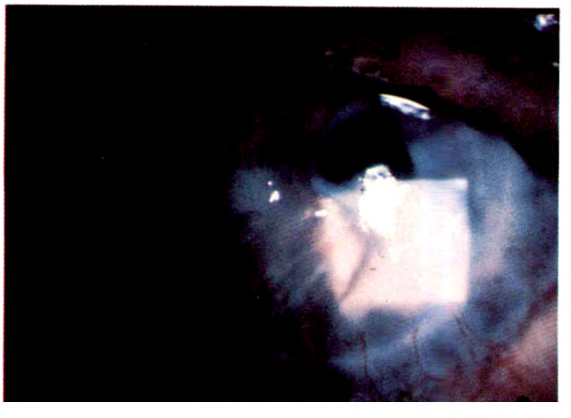
14D



14E



14F



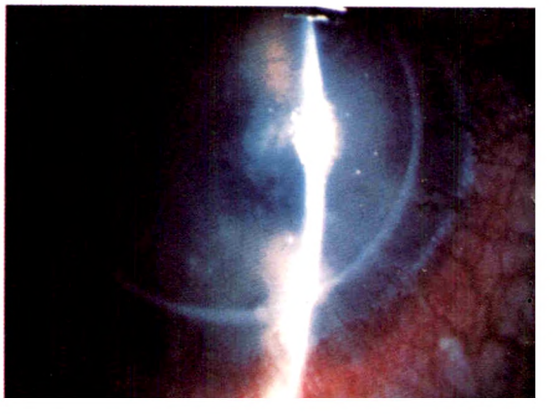


TABLE 21

INFLAMMATION PRODUCED BY NONPATHOGENIC MICROBES FOLLOWING KERATOPLASTY

| Nylon Suture Pattern | No Reaction | Infiltrate | Neovascularization | Total Cases |
|---|---|---|---|---|
| Interrupted | 1 | 27 | 23 (45%) | 51 |
| Continuous | 6 | 7 | 4 (24%) | 17 |
| Total | 7 | 34 | 27 (40%) | 68 |

occurrence of suture tract infiltrates with occasional neovascularization in some patients sutured with interrupted nylon. This reaction did not have a direct effect on graft failure in the early period; however, it could have had a role in predisposing to delayed graft reactions. Such an indigenous bacterial reaction occurred in case 10; several sutures had to be removed to arrest formation of suture tract infiltrate and neovascularization.

### CASE REPORT

Patient 10, a 56-year-old Caucasian engineering executive, experienced continual inflammatory recurrence of his atopic keratitis during the past 34 years. In the last exacerbation, his visual acuity fell to less than 20/200 and did not improve after inactivation of the inflammatory episode. Morphologic classification was 3+. An 8.0 mm penetrating keratoplasty was performed, using a single running 10-0 Ethilon suture, and four Ethilon stay sutures. The stay sutures were removed at seven days. In the second postoperative week, there was a slight persistent wound leak at the temporal graft margin so that three interrupted Ethilon sutures were placed between 2:30 and four o'clock. The subsequent clinical course was so benign that dosage of the corticosteroid drops was reduced to two times a day. By the seventh postoperative week, an interesting phenomenon had occurred: The interrupted sutures showed inflammatory infiltrate in the area of the knot extending along the suture tract and new vessel formation leading up to these sutures. The continuous suture in the same area was entirely free of inflammatory signs (Fig. 9-E). A break in epithelium with pooling of fluorescein was noted adjacent to the interrupted suture knot; the continuous suture showed no evidence of staining along its course. Conjunctival culture revealed a prolific growth of Staph. epidermidis with an occasional diphtheroid, but no pathogenic bacteria were present. After the interrupted sutures were removed, the infiltrates disappeared and the new vessels involuted (Fig. 9-F). The continuous suture was removed at four months; the patient has achieved 20/20 visual acuity with a corneal contact lens.

The extremely low incidence of graft failure in nylon suture cases, whether interrupted or continuous, negated the usefulness of the "success-failure" criterion for evaluating this reaction. This necessitated the formulation of other criteria for determining indigenous bacterial toxicity. These are: (1) infiltrate and (2) neovascularization of the suture tract, as well as subjective patient response. These phenomena occurred more frequently when interrupted sutures were used (Table 21). As already noted in case 10, the reason for this difference can be readily demonstrated with fluorescein staining. An epithelial hole is made each time an interrupted suture is tied, while only a single epithelial defect is produced with continuous suture. These epithelial breaks appear to serve as "portals of entry" for toxic or im-

←

Fig. 14 (Moore and Aronson). Delayed graft reaction. (A) Patient 12, clear graft eight and one-half months following penetrating keratoplasty. (B) Same patient, now demonstrating traumatic delayed graft reaction following cataract extraction. (C) Same patient, subsequent clear graft after penetrating keratoplasty. (D) Patient 2, demonstrating exogenously induced delayed graft reaction (limbal type) 15 months after penetrating keratoplasty (clear graft is shown in Fig. 13-D). (E) Same patient, demonstrating severe corneal ulceration following secondary infection with Staph. aureus. (F) Same patient, demonstrating subsequent clear graft four and one-half months after surgery. (G) Patient 13, endogenously induced (uveal) delayed graft reaction, demonstrating clear graft one year following surgery. (H) Same patient, demonstrating endogenously induced delayed graft reaction.

munogenic stimuli from the indigenous agent.

A distinct tissue incompatibility reaction proved extremely difficult to identify. We had only one case of graft failure in which we could rule out all other variables and speak specifically of tissue incompatibility. Theoretically, an incompatibility reaction of limbal origin would show a uniform reaction throughout the entire graft. A reaction of uveal origin would demonstrate a predominantly anterior chamber response involving primarily endothelial destruction.

Patient 11 has been included as an example of early graft reaction, even though the reaction was not identified until seven months after surgery. This outpatient failed to return for further follow-up after slightly over three months while his continuous nylon suture was still in position. He discontinued his coricosteroid medication approximately four and one-half months after surgery and first noted visual blurring shortly thereafter.* His graft failure occurred when corticosteroids were discontinued, which led us to conclude that his graft reaction originated in the early graft period. This reaction satisfies the postulated characteristics we believe a tissue incompatibility reaction should demonstrate during the early graft period; because of this we included his case history in this chapter.

* By definition, this case should be considered a delayed graft reaction and is so classified in appropriate tables.

### Case report

Patient 11, a 38-year-old Caucasian man, was an unemployed forger with history of a moderate alkali burn in his right eye two and one-half years before surgery, morphologic classification 3+. A 7.5 mm penetrating keratoplasty was secured with continuous nylon suture. The patient's postoperative course was relatively benign. When last seen, approximately 12 weeks postoperatively, he demonstrated a clear graft and was on corticosteroid drops two times a day.

When next seen, approximately seven months postoperatively, he demonstrated a markedly hazy graft throughout its entirety (Fig. 9-G). The central cornea was thickened by infiltrative edema. Of particular interest was the pattern of neovascularization of the cornea. Both superficial and deep vessels entered the cornea *between suture tracts* (Fig. 9-H), indicating that suture or exogenous toxicity did not produce this neovascularization.

On careful questioning, it was learned that the patient "had to leave the state" shortly after the 12th postoperative week "because the bunko squad was after me." He had continued using his corticosteroid drops until he ran out of them, approximately four and one-half months following surgery. Within 10 days of his discontinuance of topical corticosteroid drops, he noted photophobia and cloudy vision in the eye that was operated upon.

We started hourly topical corticosteroid drops and three times weekly subconjunctival corticosteroid injections in an attempt to see how much graft clearing would result. However, he again disappeared from follow-up.

## RESULTS

Several operative variables predominate in the early graft period which distinguish it from the remainder of the graft natural history. Perhaps the prevalent characteristic of each of these variables in this period is its acute inflammatory nature. Physiologic failure of the donor cornea is an acute process manifested within the first several weeks after surgery. The effects of surgery, whether mechanical or inflammatory, are clearly evident by the third postoperative week. Removal of the silk sutures 12 weeks after surgery mitigates this reaction. Microbes and the exogenous environment can exert their most devastating effects during this time, probably because the epithelium is incomplete and the wound not completely sealed. Finally, if tissue incompatibility is a crucial factor, the reaction is most likely to be acute during this period, as with other grafted organs.[1-3] Each of these acute reactions can operate separately or synergistically to produce graft failure. Because of this, the greatest number of graft failures occurs during the early period. With the passage of time, the ocular structure becomes normalized, and graft failure becomes less frequent.

Because of the high incidence of graft failure during the early period, we have emphasized intensive therapy during this time: corticosteroid to suppress inflammation, antibiotics to suppress exogenous microorganisms, nylon suture to prevent suture toxicity, and careful postoperative observation to ensure that irreversible graft damage does not occur. The early graft period terminates with removal of the sutures, so after this time follow-up care can be somewhat more relaxed.

*Primary donor failure*—This reflects, postoperatively, the limitations inherent in the selection of physiologically competent donor corneas. In general, we followed the precepts of Kaufman and others[4,5] in selecting donor corneas. By precluding the selection of corneas from donors over the age of 60, we hoped to have eliminated most endothelial problems related to aging.[6,7] Similarly, by using eyes as soon as possible after death, the effects of time and temperature should be reduced.[8,9] Corneal viability was evaluated preoperatively by biomicroscopic examination of the tissue. Obviously, evidence of edema, scarring, or endothelial change disqualified a donor cornea. There was one case of acute donor failure in 163 penetrating keratoplasties, an incidence of approximately 0.7%. This failure was recognized rapidly, and the patient was regrafted with relatively little morbidity in the second postoperative period (case 1). Ideally, this episode could have been avoided. However, the problem posed by such a donor failure is not particularly severe and, as in case 1, can be easily rectified. Although it would be preferable to have a more effective technique to evaluate the physiologic state of donor tissue, as has been suggested by others,[10,11] we believe that the relatively simple protocol followed in this series adequately eliminates nonviable donor corneal tissue. Less selective criteria (e.g., using eyes from patients of any age or for prolonged periods after death) would necessitate a more sensitive technique for evaluation of donor physiology.

To evaluate surgery as a variable, a single, standardized procedure had to be used in all cases until a series of adequate size was accumulated, after which any change in technique could be compared with the original procedure. To standardize this procedure, one of us (T.E.M., Jr.) either performed or assisted at the surgery in every case in the series and closely controlled postoperative management. This supervision ensured quality control throughout the course of the series. The comparative study between private and resident surgery reveals no significant difference in results (Table 15).

*Mechanical problems secondary to surgical inconsistency*—These problems occurred more frequently in the first chronologic surgical period (1965–67), became less frequent in the second period (1967–68), and were ex-

tremely infrequent with the adoption of nylon suture (Table 14). The rate of surgical complications closely parallels the graft success rate during these chronologic periods. In the first and second periods, while silk sutures were used, it seems likely that technical proficiency of the surgical team improved. However, the sharp increase in success rate when nylon suture was introduced implicates the suture as the more significant variable in these results.

The incidence of inflammation has been correlated with the extent of the surgical procedure performed (Tables 16 and 17). In general, the severity of the intraocular surgery had little effect on the outcome of the graft itself. (When limited to the nylon suture group, however, all three failures were in the group undergoing the most extensive surgery). When the type of procedure is compared with other ocular complications, the simple keratoplasty demonstrated the lowest number of non-corneal complications. However, overall visual acuity was approximately the same in the patients undergoing penetrating keratoplasty alone and those in whom the procedure was combined with cataract extraction (56 vs 61%). Of nine cases undergoing subsequent cataract extraction, three experienced some degree of endothelial disruption which led to graft failure. This observation, coupled with the high rate of success for the combined procedure, supports the contention that the combined procedure is preferable when cataract is present.[12,13]

There was a much higher incidence of complications when keratoplasty was combined with anterior chamber revision. These eyes frequently presented with severely altered internal and external structure and elevated intraocular pressure: eight of 17 eyes had vision-reducing disease. The high complication rate may be a manifestation of the initial disease—e.g., 12 eyes had suffered corneal perforations before surgery. Generally speaking, variation in surgical procedure had relatively little effect on the eventual outcome of the graft. However, eyes which had undergone extensive intraocular surgery demonstrated an increased incidence of intraocular complications.

*Suture toxicity*—Of all the variables evaluated within this series, suture toxicity appeared to be the most important single cause of graft failure. As noted in Table 19, when 10-0 Ethilon suture was used routinely, early success rates for all grafts improved from 81 to $> 95\%$. This change was not particularly pronounced in the cases with good prognosis, where success rates improved from 92 to 100%, but was markedly pronounced in the group with poor prognosis, where success rates increased from 73 to 93%.

Two individual cases demonstrate this difference in degree of suture toxicity, where interrupted 8-0 silk, 9-0 silk, and 10-0 nylon sutures were used alternately in suturing the donor button (Fig. 8-E and F). The reaction was considerably more severe to silk suture than to nylon. This type of experiment has been undertaken by other investigators[14,15] who reported similar results.

The emergence of suture toxicity as such an important factor in graft failure prompted us to determine the nature of suture toxicity. In a series of sequential in vivo studies,[16,17] we demonstrated the toxic nature of silk suture and the relatively inert characteristic of the nylon suture. In our initial experiments in rabbits, nylon suture appeared less toxic than the other sutures tested (8-0 silk, 9-0 silk, and 7-0 collagen); however, toxicity was noted with time. It appeared that the origin of this inflammatory reaction was the indigenous (nonpathogenic) bacteria of the conjunctival sac, with the suture tract providing an entrance to corneal stroma.

To confirm this inflammogenesis, the same experiment was repeated in germ-free guinea pigs. All sutures were tested again in guinea pig corneas, and this time there was no evidence of suture toxicity for 10-0 Ethilon.[17] However, some degree of toxicity was demonstrated in all other sutures.

Although silk suture toxicity was de-

quiescent, evidence for its past activity was sometimes hard to detect. Disagreement occurred most frequently in these groups.

Difficulty in separating 3 and 4+ cases led us to adopt a supraclassification which cancelled out the described error. Thus, morphologic groups were combined into good and poor prognosis categories. The good prognosis group (0, 1A, 1B, and 2+) at most demonstrated mild neovascularization and mild intraocular involvement. The poor prognosis group (3 and 4+) showed severe neovascularization and severe intraocular involvement. Classified in this fashion, overall early graft success rates were appreciably better in the good prognosis groups (95%) than in the poor prognosis groups (82%). This proved to be a very significant separation when statistically evaluated by discriminant function.

In summary, the clinical and morphologic classification appears to offer a relatively accurate severity gradient of structural alteration in the recipient cornea. By circumscribing other parameters which are difficult to grade (e.g., etiology), a high degree of reproducibility can be achieved. Correlation between morphologic group and prognosis proved to be extremely accurate.

Etiologic classification proved more difficult. Diagnosis was reasonably accurate for herpes simplex, herpes zoster, bacterial ulcers, aphakic bullous keratopathy, and keratoconus; however, such categories as idiopathic stromal keratitis and chemical or physical keratitis are markedly heterogeneous. This variation becomes particularly pronounced in evaluation of morphologic severity of the lesion. While most herpes simplex keratitis patients who go on to keratoplasty fall within the 3 or 4+ morphologic category (Table 3), patients with idiopathic stromal keratitis ranged from 2 to 4+ and those with chemical and physical injuries range from 1 to 4+. In our opinion, this classification does not adequately describe disease severity. Instead, these categories reflect the morphologic severity produced by a particular etiologic agent. In herpes simplex, seven of eight graft failures were in the 4+ category, while the eighth was in the 3+ category. Similarly, all interstitial stromal keratitis and chemical or physical trauma graft failures were in the 3 or 4+ groups. The 2+ cases with each of these diagnoses always resulted in successful grafts. Therefore, it would appear that the principal value of etiologic diagnosis for these groups lies in the morphologic severity which a particular etiologic agent has produced.

The question must be raised whether any etiologic category has usefulness as a subcategory within the morphologic scheme. Initially, aphakic bullous keratopathy was separated from the remainder of 1+ diagnoses because (1) distinct evidence of previous intraocular inflammation was identifiable, and (2) success rates seemed to be lower than in the 1A+ and 2+ categories. On close analysis, however, all early 1B+ graft failures occurred within the first surgical period (Table 14) in which silk suture was used. The most recent 21 cases have all resulted in early graft success, so that it seems likely that the 1B+ subdivision may not be justified.

A similar circumstance arises in chemical and physical keratitis. Generally, the prognoses given for the chemical keratitises have been poor, much worse than for any other category.[30,31] Overall, early graft results have not supported this (Table 9). If severe alkali cases are separated from the series, our results still do not bear this out. (In this circumstance, our results are six successes out of seven in the early period.) Pretreatment with heparin, which appears to revascularize ischemic zones, combined with high-dosage topical corticosteroid therapy, appears to enhance the chance for graft success. With time, however, alkali keratitis patients seem to be prone to delayed graft failure.

Although etiology is of less value than morphologic classification for graft prognosis, in the event of infectious etiology it is necessary for selection of appropriate, spec-

ific pre- and postoperative medication. As already noted, patients were treated specifically for each infectious agent identified during the early graft period. The antimicrobial agent is not discontinued until sutures have been removed and the epithelium is completely intact. The reason for this is culture evidence that certain individuals show a predilection for recurrence of specific bacteria or virus when antimicrobials are discontinued, e.g., herpes simplex, staphylococcus, and pseudomonas.[32-35] Also, corticosteroids probably allow enhancement of microbial proliferation.[36,37] This combination of events in the presence of altered structure could lead to a severe inflammatory response (as in patient 9).

Measurement of early IgG appeared to be particularly useful as a prognostic index to the severity of inflammation which could be anticipated in a forthcoming graft procedure. As Table 10 indicated, this correlation was more valuable in conjunction with the clinical and morphologic classification. Total IgG correlation with inflammatory response was less exact. Other immunologic factors were unrelated to graft-induced inflammation.

Since adopting early IgG as a therapeutic index for prospective graft patients, a group of selected patients have not been preoperatively treated with corticosteroid. The overall results in this selected group of patients are similar to those in the series that was treated prophylactically (Table 12). Statistical evaluation by discriminant function revealed prognostic significance for early IgG in silk suture cases during the early graft period (Table 22). When analysis is made on all cases (silk and nylon), prognostic value of early IgG during the early graft period is no longer statistically significant (Table 23). This is readily reflected by the number of early graft failures encountered when nylon suture is used; whereas 18 cases failed with 8-0 virgin silk, only three cases failed when nylon was used. Undoubtedly, the employment of nylon suture has allowed cases to succeed which would have failed with silk.

The exact function of early IgG is un-

TABLE 22

DISCRIMINANT FUNCTION ON OUTCOME OF CORNEAL TRANSPLANT: ALL SUTURES

| | All Cases | | Cases with Known Early IgG | |
|---|---|---|---|---|
| | Early Outcome | Late Outcome | Early Outcome | Late Outcome |
| Morphologic classification | 0.005* | 0.004* | 0.005† | 0.005* |
| Microbial pathogen | −0.003 | 0.011 | −0.003 | 0.012 |
| Surgical procedure | −0.005 | −0.005 | −0.005 | −0.007 |
| IgA | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| IgM | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| IgG | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| Early IgG | −0.002 | >0.0005 | −0.002 | −0.001 |
| Wound | 0.040* | 0.019† | 0.041* | 0.020† |
| Glaucoma | 0.004 | 0.003 | 0.003 | 0.004 |
| Retinal detachment | −0.004 | −0.004 | −0.004 | −0.003 |
| Secondary membrane | 0.032* | 0.017† | 0.032* | 0.021† |
| Unrelated variable | −0.004 | −0.008‡ | −0.005 | −0.011 |
| Surgeon | −0.005 | 0.005 | −0.004 | 0.006 |
| Type of suture | −0.013† | −0.007 | −0.014† | −0.011† |
| F | 6.840* | 4.302 | 5.961* | 4.491* |
| DF | 14 and 148 | 14 and 131 | 14 and 131 | 14 and 118 |

* Significant at $p \leq 0.001$.
† Significant at $p \leq 0.01$.
‡ Significant at $p \leq 0.05$.

TABLE 23

DISCRIMINANT FUNCTION ON OUTCOME OF CORNEAL TRANSPLANT: 8-0 VIRGIN SILK SUTURE

| | All Cases | | Cases with Known Early IgG | |
|---|---|---|---|---|
| | Early Outcome | Late Outcome | Early Outcome | Late Outcome |
| Morphologic classification | 0.014* | 0.010* | 0.016* | 0.010† |
| Microbial pathogen | −0.011 | 0.016 | 0.012 | 0.016 |
| Surgical procedure | −0.019 | −0.021 | −0.018 | 0.020† |
| IgA | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| IgM | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| IgG | >0.0005 | >0.0005 | >0.0005 | >0.0005 |
| Early IgG | −0.007‡ | −0.003 | −0.007 | −0.003 |
| Wound | 0.082* | 0.035 | 0.084* | 0.034† |
| Glaucoma | >0.0005 | 0.008 | >0.0005 | 0.007 |
| Retinal detachment | >0.0005 | 0.014 | −0.007 | 0.012 |
| Secondary membrane | 0.041‡ | 0.028 | 0.040‡ | 0.026 |
| Unrelated variable | 0.0005 | −0.013 | 0.002 | −0.014 |
| Surgeon | 0.008 | 0.004 | −0.009 | 0.005 |
| F | 5.949* | 3.779* | 5.493* | 3.224* |
| DF | 13 and 81 | 13 and 78 | 13 and 75 | 13 and 72 |

* Significant at $p \leq 0.001$.
† Significant at $p \leq 0.01$.
‡ Significant at $p \leq 0.05$.

known. At the time of our initial report,[38] we believed that IgA may also have been involved. Subsequent findings have indicated that only the early zone of IgG is related to graft prognosis.[39,40] In the past, we hypothesized that the early range of IgG may represent a measure of overall subclinical inflammation within the body, whereby in such persons, serum levels would be diminished because of molecular binding of the early IgG molecule at the site of inflammation. Currently, this is the only plausible explanation we have for the correlation between reduced early IgG and prospective graft-induced inflammation.

In conclusion, certain aspects of these studies have led to revision of our methods of procedure. While methods of patient selection and selection of donor corneas remain unchanged, several other factors have changed, and these are as follows:

*Selection of surgical procedure*—A penetrating keratoplasty is preferably between 7.0 and 8.0 mm in diameter. The extent of intraocular surgery is now dictated by the conditions encountered at surgery. If a cataract is also present, a combined procedure is undertaken.

*Sutures and suturing technique*—Four interrupted 10-0 nylon sutures are placed at three, six, nine, and 12 o'clock, and these are removed one week postoperatively. A continuous 10-0 nylon suture is tied in the 12 o'clock meridian, well away from the donor cornea and the cut ends are inserted either beneath bulbar conjunctiva or into corneal stroma and allowed to remain in position for 16 to 20 weeks.

*Corticosteroid therapy*—Prophylactic use of corticosteroid is determined by the immunomorphologic table (Table 4). The corticosteroid protocol remains unchanged.

Antibiotic therapy, the use of mydriatics, and postoperative care remain unchanged. Patients are given either a spectacle correction or a corneal contact lens,[41] and are followed according to the described postoperative schedule.

Once again, we should emphasize that while this is our current protocol, it is subject to change as we gain more experience with the penetrating keratoplasty.

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As already noted, delayed graft reactions are divided into mechanical or inflammatory types. The mechanical reaction, related to surgery, requires a secondary event which interferes with the normal physiologic processes of the corneal endothelial cell. In our experience, cataract surgery has most often led to this phenomenon.

In our case 12, described below, the patient had a relatively uneventful postsurgical course. However, nine months after the initial keratoplasty, a lens extraction was performed. Following this, the patient developed epithelial edema superiorly which gradually went on to involve the entire visual axis (Fig. 14-A and C).

### Case report

Patient 12 was a 58-year-old Italian American man, first seen and treated for active herpes simplex stromal keratitis approximately four years earlier. An initial penetrating keratoplasty was performed after inactivation of the herpetic infection, and a clear corneal graft was achieved (Fig. 14-A). Nine months following this graft, an intracapsular cataract extraction was performed. At the time of surgery, the lens capsule forceps inadvertently rubbed the endothelial surface of the cornea. Following surgery, a zone of corneal edema was present which was not responsive to corticosteroid therapy. This localized area gradually progressed to involve the entire donor cornea; following this, secondary neovascularization occurred (Fig. 14-B). A subsequent penetrating keratoplasty was successful, and the patient achieved >20/25 visual acuity with a corneal contact lens (Fig. 14-C).

In reviewing this case, the pathogenetic sequence was traumatization of donor endothelium produced by entering the anterior chamber with capsule forceps. Surgery subsequent to keratoplasty must be extremely meticulous, with every effort being made to avoid contact with donor endothelium.

The inflammatory cases comprise two general types, either of which can progress to graft failure. Patient 2, already described, experienced a severe "cold" 15 months following keratoplasty; visual blurring occurred in the grafted eye, but the patient did not seek medical aid for nine days following this event. Despite high-dosage corticosteroid therapy, delayed graft failure could not be reversed (Fig. 14-D through F).

### Case report

Patient 2 retained a clear corneal graft for 15 months. A cataract was extracted at six months (Fig. 13-D). During the 15th month, he presented with loss of vision of approximately 10 days' duration. This occurred during the Asian flu ($A_2$) epidemic of 1968, and the patient complained of severe upper respiratory symptoms as well as "itchy" eyes.

On ocular examination, he demonstrated bilateral follicular conjunctivitis with acute congestive changes superimposed upon his bulbar conjunctiva. His cornea was markedly inflamed, showing engorgement of vessels in the host cornea and dense inflammatory infiltration of the donor cornea (Fig. 14-D). The opposite eye demonstrated follicular conjunctivitis and fine epithelial stippling of the cornea. The patient also demonstrated an acute pharyngitis. He was immediately hospitalized and started on hourly topical and daily subconjunctival corticosteroid injections. After one week of this therapy, he demonstrated some stromal clearing; however, he showed persistent epithelial edema, indicating endothelial destruction. The patient was continued on corticosteroid for another week, at the end of which time corticosteroid was discontinued and he was classified as a delayed graft failure.

When next seen (approximately eight months later), the graft had become secondarily infected with Staph. aureus, and he demonstrated severe inflammation with ulceration of donor graft tissue (Fig. 14-E). This was controlled with topical Neosporin and corticosteroid therapy. The patient was regrafted and maintained a clear graft for eight months following surgery (Fig. 14-F). He again reported to the clinic with severe opacification and neovascularization of both the donor and host corneas. On questioning, he stated that he first noted visual blurring two and one-half weeks earlier. He demonstrated a prolific growth of Staph. aureus on conjunctival culture. At present, he is receiving topical Neosporin and corticosteroid therapy.

This case followed the corneal pattern of inflammation—i.e., both in the central spreading of the limbal inflammation, and the presentation of the inflammation as keratoconjunctivitis.

The uveal pattern of inflammation is demonstrated in patient 13. The patient presented with an acute iritis in one grafted eye. The involved left eye was blind and served as an autograft donor to the opposite right eye; the left eye was simultaneously allo-

TABLE 24

TREATMENT SUCCESS IN DELAYED GRAFT REACTIONS

| No. Patients | No. Attacks | Graft Clear after Treatment | Graft Failures | % Treatment Success |
|---|---|---|---|---|
| 36 | 64 | 48 | 16 | 75 |

grafted. Because her blindness interfered with the recognition of symptoms, the patient did not present for therapy for several weeks after the corneal reaction started. By then, permanent endothelial change had occurred and could not be reversed with corticosteroid therapy (Fig. 14-G through H).

CASE REPORT

Patient 13 was a 51-year-old Caucasian woman with history of congenital cataract and blindness of more than 10 years' duration. Ocular examination revealed a blind left eye secondary to a retinal detachment with a clear cornea and a severely scarred right cornea. Both eyes demonstrated searching nystagmus.

Combined penetrating autograft (left to right cornea) and allograft (to left cornea) were performed using interrupted 8-0 virgin silk suture. Both grafts were successful (Fig. 14-G). The patient showed periodic bouts of inflammatory infiltrate into the inferonasal margin of the right autograft and was treated with topical corticosteroid. During one such period, she suffered a severe upper respiratory infection (URI). About two weeks after the onset of this attack, she noted that her blind left eye was injected and painful and she then presented for treatment. The left eye showed a marked papillofollicular reaction of the bulbar conjunctiva, ciliary injection, a hazy edematous cornea, and a 3+ iritis. Dense KP were noted on the posterior corneal surface (Fig. 14-H). The right conjunctiva demonstrated a fine follicular reaction; the cornea and anterior chamber remained free of inflammatory disease. The patient was using prednisolone acetate 1% drops four times a day in this eye. Hourly topical corticosteroid drops and daily subconjunctival corticosteroid injections were started to the left eye and continued for one week, the drops being continued for a second week. The iritis resolved rapidly, with disappearance of the KP. However, the endothelium must have been compromised, for epithelial and stromal edema remained. Since the eye was blind, a second keratoplasty was not contemplated. The patient was seen at regular intervals to prevent superinfection of this cornea.

Frequently, delayed graft reactions could be treated successfully (Table 24); 75% of delayed reactions were reversible with topical and subconjunctival corticosteroid therapy. Patient 14 demonstrates exogenous origin of disease in which the patient presented soon after the onset of ocular signs. Intensive corticosteroid therapy reversed his delayed reaction with a good visual result (Fig. 15-A through D).

CASE REPORT

Patient 14 was a 27-year-old Chilean man with a history of stromal keratitis following a thermal injury. Following a total lamellar keratectomy to remove a pseudopterygium, morphologic classification was 3+. A penetrating keratoplasty was performed using 8-0 virgin silk suture with a successful result. Visual acuity was 20/25 corrected with a corneal contact lens (Fig. 15-A).

Nine months after the keratoplasty, the patient presented complaining of blurred vision. He demonstrated an acute congestive conjunctivitis bilaterally. Culture revealed a prolific growth of Staph. epidermidis. The left eye showed marked vascular engorgement of the temporal vessels in the recipient cornea, with extension of infiltrate into the donor graft. The donor graft demonstrated inflammatory edema throughout (Fig. 15-B).

The patient was immediately started on topical and subconjunctival corticosteroid, the latter being given every other day for one week. After 11 days of hourly medication, he showed marked improvement (Fig. 15-C) and by three weeks the eye appeared clear; medication was then tapered to one drop a day. Four months after this episode, visual acuity returned to 20/25 (Fig. 15-D).

One year later he experienced another episode of blurring and immediately flew to San Francisco for evaluation. This time, he demonstrated an acute exudative conjunctivitis (left eye more severe than the right eye). Staph. aureus grew on culture. The corneal involvement was limited to the area adjacent to vascularization of the host cornea. Combined topical and subconjunctival corticosteroid resulted in a rapid remission. The area of vascular origin in the recipient and graft was attached to the palpebral conjunctiva by symblepharon. It was decided to sever this adhesion surgically with the expectation that the vessels in the host cornea would involute and no longer predispose the eye to delayed reactions.

Patient 15 provides an example of a grafted eye that had attacks of recurrent uveitis for several years. She presented with an acute iritis and marked graft edema secondary to KP which cleared rapidly on topical and subconjunctival corticosteroid therapy (Fig. 15-E through H).

### CASE REPORT

Patient 15 received a penetrating keratoplasty for severe herpes simplex stromal keratitis with perforation, morphologic classification 4+ (Fig. 15-E). Following surgery, she had a successful result with a clear donor graft (Fig. 15-F). However, because of a mature cataract, vision was unimproved.

Five months following her keratoplasty, she experienced pain and redness of her eye with a concomitant severe URI. Ocular examination revealed bilateral follicular conjunctivitis, more severe on the right side. The right eye demonstrated limbal injection and edema of the donor graft. A moderately severe iritis was noted in the anterior chamber with 2 to 3+ cellular reaction (Fig. 15-F). The opposite eye showed fine epithelial stippling of the cornea.

The patient was started on topical and subconjunctival corticosteroid for one week and demonstrated a dramatic improvement. The anterior uveitis cleared rapidly; in two to three weeks, the graft cleared completely (Fig. 15-H). Three months later, her lens was extracted; visual acuity was >20/30 with a corneal contact lens (Fig. 15-H).

The variable which principally influences success or failure in a delayed graft reaction is duration of inflammation prior to therapy (Table 25). If patients presented within 24 hours of inflammatory onset, delayed graft reactions could be routinely reversed, with good visual results. When presentation was within seven days of onset, in 94% the process was reversible; however, after inflammation had been present for more than a week, the prospects for reversal became extremely poor (50%). Of particular interest is the fact that in six patients who experienced two or more attacks, but who presented immediately after inflammatory onset, the process could be reversed. However, when treatment was delayed for one to two weeks, grafts went on to failure. It is difficult to determine exactly how long inflamma-

TABLE 25

DURATION OF DELAYED GRAFT REACTION BEFORE CORTICOSTEROID TREATMENT

| Time Elapsing before Therapy | No. Patients Reacting | No. Treatment Failures | % Failure |
|---|---|---|---|
| 24 hours or less | 18 | 1 | 6 |
| One to seven days | 22 | 3 | 14 |
| Over seven days | 24 | 12 | 50 |
| Total | 64 | 16 | 25 |

TABLE 26

ROLE OF STIMULUS IN DELAYED GRAFT REACTIONS

| Stimulus Type | Total Cases | No. Attacks | Graft Failures | |
|---|---|---|---|---|
| | | | No. | % |
| Trauma | | | | |
| Intraocular (surgical) | 3 | 3 | 3 | 100 |
| Extraocular | 2 | 2 | 0 | 0 |
| Total | 5 | 5 | 3 | 60 |
| Inflammatory—Exogenous | | | | |
| Bacteria (pathogenic) | 15 | 20 | 7 | |
| Bacteria (indigenous) | 3 | 7 | 0 | |
| Herpes simplex virus | 2 | 4* | 1 | |
| Upper respiratory virus | 10 | 18 | 3 | |
| Allergy response | 2 | 3 | 1 | |
| Total | 32 | 51 | 12 | 24 |
| Inflammatory—Indigenous | | | | |
| Uveitis | 4 | 6 | 1 | 17 |
| Inflammatory—Idiopathic | 6 | 7 | 3 | 43 |

* Delayed graft reactions were demonstrated by 12 patients with herpes simplex; in only two of these patients could recurrence of herpes simplex virus be identified by electron microscopy.

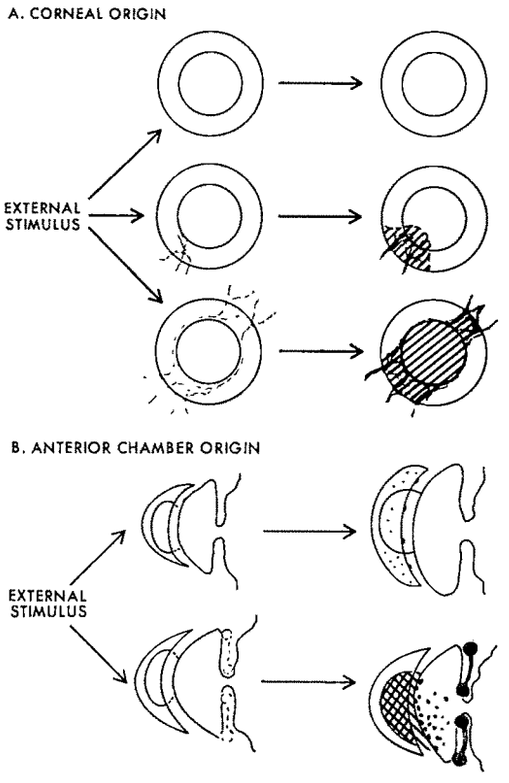



Fig. 16 (Moore and Aronson) Pathogenesis of the delayed graft reaction. (A) Corneal origin. (B) Anterior chamber origin.

tion can remain untreated without resulting in permanent endothelial decompensation. Undoubtedly, there is some degree of individual variation, but the critical time in this study was approximately seven days.

Factors which may predispose to delayed graft reactions are (1) an adequate stimulus, (2) variation in host response, and (3) severity of structural alteration.

In attempting to evaluate the origin and nature of the stimulus which provoked the recurrent inflammatory episode, we were able to identify a series of different etiologic agents (Table 26). The traumatic causes were easily classified into surgical (intraocular) and other (extraocular) trauma. The former produced graft failure, but the latter may not. The inflammatory delayed graft reactions have been divided into exogenous and endogenous stimulus pathways. The exogenous group again subdivided into bacterial (pathogenic and indigenous), viral (herpes simplex and upper respiratory infections, and nonreplicating topical allergens). Endogenous inflammations presented initially as uveitis; etiology for these attacks was seldom identified, although almost every episode followed a systemic illness. Finally, a small group of cases, apparently of exogenous onset and of unkown etiology, have been identified as idiopathic. All delayed graft failures in this group occurred in patients with chemical injuries. Strong criteria for diagnostic relationship were present

TABLE 27

ROLE OF STRUCTURE IN DELAYED GRAFT FAILURE

| Preoperative Morphology | Total Cases | Delayed Reaction | | Delayed Failure | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| 0+ | 26 | 3 | 12 | 1 | 4 |
| 1A+ | 1 | 1 | 100 | | |
| 1B+ | 10 | 3 | 30 | 1 | 10 |
| 2+ | 12 | — | | — | — |
| Total | 49 | 7 | 14 | 2 | 4 |
| 3+ | 29 | 13 | 45 | 5 | 17 |
| 4+ | 51 | 22 | 43 | 9 | 18 |
| Total | 80 | 35 | 58 | 14 | 18 |
| Grand Total | 129 | 42 | 33 | 16 | 12 |

in all but the group in which history and other clinical evidence of upper respiratory disease served as bases for diagnosis. Five of the six patients in the idiopathic group demonstrated some degree of corneal vascular insufficiency, which probably explains the graft failure. In no case, however, were we able to demonstrate a delayed reaction solely attributable to tissue incompatibility.

Immunologically, patients with delayed graft reactions and delayed graft failures showed some increase in IgG, early IgG, and IgM, when compared with the nonreacting patients (Table 7). However, this increase could not be interpreted as a significant change. Similarly, protein electrophoresis and qualitative electrophoresis showed no particular abnormalities in patients with these groups. Since no hypogammaglobulinemic patients were identified in these groups, it would appear that immune competence is required in order to produce a delayed graft reaction.

TABLE 28

POSTOPERATIVE EVALUATION OF STRUCTURE IN RELATIONSHIP TO OCCURRENCE OF DELAYED GRAFT REACTIONS

| Preoperative Classification | Total Cases | Postoperative Classification Vessels | | | Previous Uveitis |
|---|---|---|---|---|---|
| | | Absent | Mild | Moderate | |
| 0+ | 3 | | 1* | 2 | 1* |
| 1A+ | 1 | | 1* | | 1* |
| 1B+ | 3 | | | 3 | |
| Total | 7 | | 2 | 5 | 2 |

* Both cases with mild corneal changes had a history of previous uveal involvement.

At the end of the 12-week graft period, the structural integrity of the cornea proved to be of greatest significance with respect to predisposition toward recurrence of inflammation.

Corneal host changes after keratoplasty were classified as (1) absent, (2) segmental,

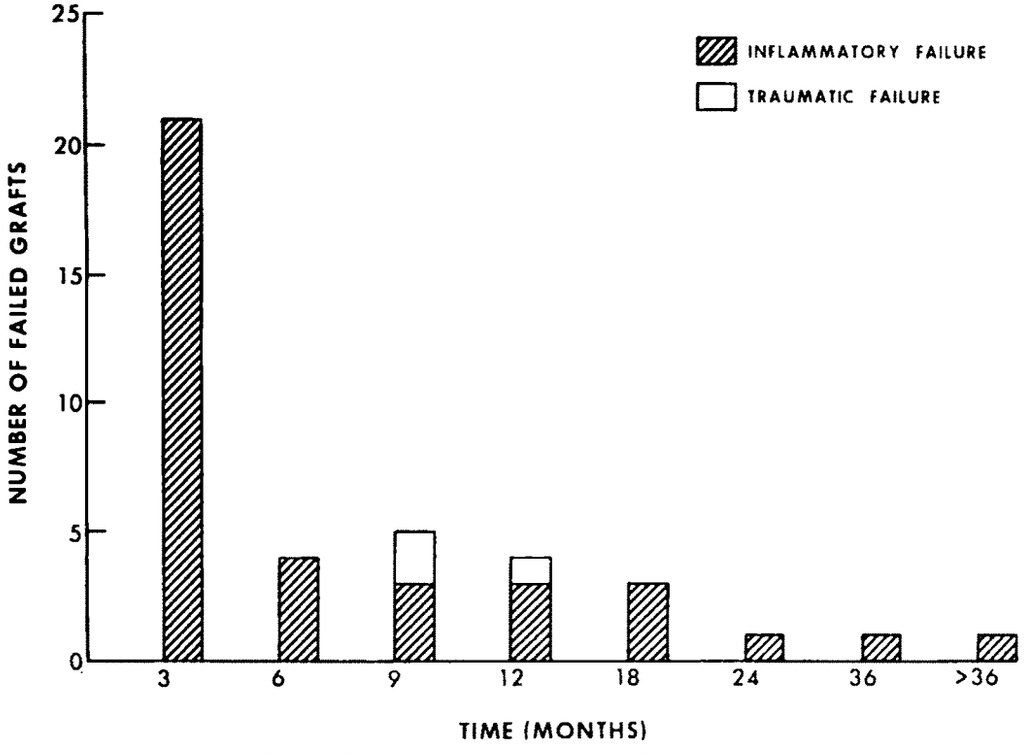



Fig. 17 (Moore and Aronson). Onset of graft failure following surgery.

TABLE 29

ASSOCIATION OF SOCIOECONOMIC FACTORS WITH DELAYED GRAFT FAILURE

| Patient Series | Total Cases | Prognosis | | Delayed Reactions | | Delayed Failures | |
|---|---|---|---|---|---|---|---|
| | | Good | Poor | No. | % | No. | % |
| Private | 75 | 27 | 48 | 17 | 23 | 7 | 9 |
| UC | 33 | 24 | 9 | 10 | 30 | 2 | 6 |
| SFGH | 17 | 3 | 14 | 15 | 88 | 7 | 41 |
| Total | 125 | 54 | 71 | 42 | 34 | 16 | 13 |

or (3) generalized (Fig. 16). The degree of postoperative structural change roughly paralleled the preoperative morphologic classification, so that a preoperative 0+ patient will frequently show little or no neovascularization of the *host* cornea; naturally, a 4+ cornea always shows severe neovascularization of the host. Correlation of preoperative classification and occurrence of delayed graft reactions reveals that the majority of reactions occurred in the proper prognosis groups (3+ and 4+) (Table 27). When structural evaluation included the postoperative recipient cornea, delayed graft reactions correlated most closely with generalized recipient vascularity. This evaluation was more useful in groups with good prognosis, since initial corneal vascularization was either superficial or absent. Of the six patients who demonstrated delayed graft reations in the good prognosis groups, four demonstrated generalized vascularization of the recipient cornea; the other two showed segmental corneal vascularization, but had experienced many attacks of recurrent iritis (Table 28). Evidence of previous uveitis also predisposed such individuals to delayed reactions of the uveal pattern (Fig. 17).

The final variable studied was the relationship of socioeconomic status to delayed graft disease (Table 29). The overall recurrence rate in the indigent population (SFGH) substantially exceeded the recurrence rate in private and UC clinic patients, 88 to 23 to 30%. Similarly, graft failure as a result of delayed reactions occurred most frequently in the SFGH population (41 to 9 to 6%). This observation may be explained by the marked delay the SFGH patients exhibited in reporting their ocular symptoms (SFGH—11 days, UC—3.1 days, private patients—2.3 days).*

* This average of reporting time includes case 13, the patient with a blind grafted eye who came for treatment two weeks after the onset of symptoms, but excludes case 11, the criminal forger, who did not return for therapy.

Fig. 15 (Moore and Aronson). Delayed graft reaction. (A) Patient 14, demonstrating a clear graft four months after penetrating keratoplasty. (B) Same patient, demonstrating an exogenously induced delayed graft reaction nine months following surgery. (C) Same patient demonstrates corneal clearing after 11 days of corticosteroid therapy. (D) Same patient four months after inflammatory episode. The cornea has cleared and visual acuity has returned to the preinflammatory level (20/25). (E) Patient 15, preoperative photograph demonstrating central corneal perforation. (F) Same patient, postoperative photograph (six months) demonstrating clear penetrating graft (G) Same patient, nine months postsurgery, demonstrating a delayed graft reaction (uveal type). (H) Same patient after clearing of delayed graft reaction and subsequent lens extraction.

monstrable in vivo, the nature of the toxic reaction still remained obscure. In the past, we demonstrated a toxic corneal reaction to acacia extract[18] in which gamma globulin and complement were bound directly by the toxic agent but not by immunologic identification, leading to an acute inflammatory reaction. Using this as a model, we attempted to evaluate qualitative gamma globulin binding by silk and nylon sutures; strands of silk suture bound more than six times the amount of gamma globulin bound by the nylon.[19] This finding indicates that suture toxicity represents nonspecific binding of gamma globulin with subsequent complement binding, which in turn feeds into the acute inflammatory pathway.[19] The differences in toxicity between silk and nylon suture can readily explain the divergence in results obtained in our human graft series.

The potential hazard of the pathogenic microbe in corneal grafting has long been recognized[20,21] and probably accounts for routine saturation of the donor cornea with an antibiotic solution[22,23] as well as pre- and postoperative prophylactic antibiotic therapy.[24] The typical morphologic lesion, the suture tract abscess, correlates accurately with identification of pathogenic bacteria. It is interesting to note that this type of lesion occurs rather infrequently (in approximately 2.5% of cases) and, if recognized early, the pathologic process can be reversed with high-dosage topical antibiotic and corticosteroid therapy. As noted in our series, no cases of early graft failure could be attributed to pathogenic bacterial involvement.

The role of the virus in the early graft period is more difficult to evaluate, principally because of problems associated with primary virus isolations. In our series, primary virus isolation was attempted in only a few cases. Viral disease was usually diagnosed "after the fact" by electron microscope identification of the herpes simplex virus in failed donor or recipient tissue, or by a strongly presumptive diagnosis of herpetic endophthalmitis. (Since these were our critieria for diagnosis, it is not surprising to find that all cases with a positive virus diagnosis during the early graft period had failed.) By the criteria used, less than 8% of herpes simplex cases submitted to surgery demonstrated herpes simplex involvement during the early graft period. However, all cases suspected of this diagnosis preoperatively were treated in the postoperative period with topical IUDR and corticosteroid, and this could have suppressed virus proliferation. Evidence of other viral involvement was not present during the early graft period.

The role of indigenous (nonpathogenic) bacteria during the early graft period is of particular interest. Evidence for this toxicity reaction was based upon differences in the degree of morbidity between continuous and interrupted nylon suture cases (Table 21). The interrupted suture cases frequently demonstrated suture tract infiltrates as well as neovascularization, while the continuous suture cases showed only infiltrate at the site of the knot. This is exemplified in case 10, where both interrupted and continuous sutures were used but only the interrupted sutures demonstrated inflammogenesis. The microbes most frequently demonstrated on conjunctival culture were Staph. epidermidis and diphtheroids. We believe that the breaks in the epithelium caused by the suture serve as the "portal of entry" for bacterial or other stimuli.

This type of reaction has frequently been referred to in the literature as an irritation or irritative reaction.[25,26] The mechanism of toxicity is presumed to be the continuous movement or rubbing of the knot against the cornea. This mechanical stimulation produces corneal tissue necrosis, which sets up a subsequent inflammatory response. To refute this classic idea of irritation, we again returned to the germ-free guinea pig.[27] Animals were initially sutured with a single interrupted 10-0 nylon suture in a germ-free tank and allowed to remain in this condition for up to three months, during which time no inflammatory reaction occurred. Following this, the animals were infected with Staph. epidermidis. Within five days, severe

inflammatory signs occurred in the sutured eyes.

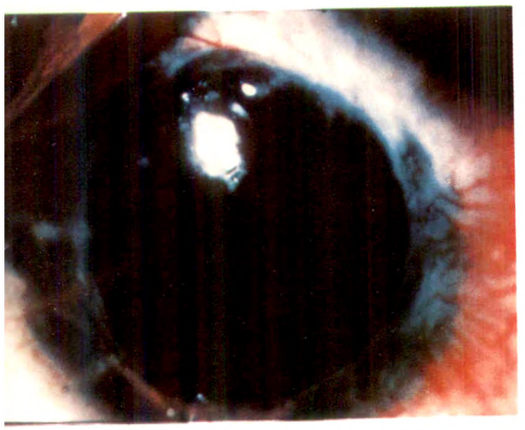
Animals' conjunctivae were recultured at this time and they demonstrated the presence of only the single nonpathogenic microbe. This experiment demonstrates the potential toxicity of indigenous bacteria under appropriate conditions of structural alteration. Indigenous bacterial toxicity, not mechanical irritation, is the most likely cause of inflammation when interrupted nylon sutures are used.

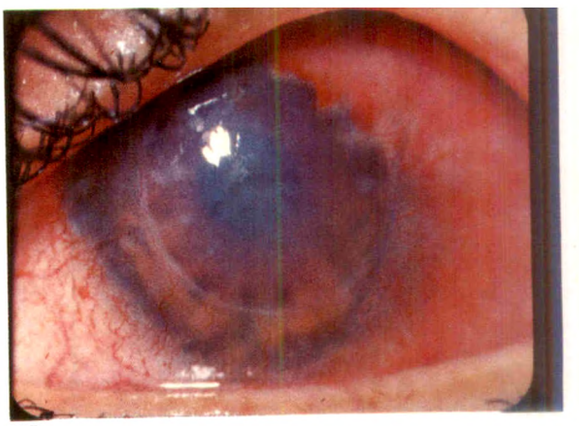
As noted earlier, we were able to identify a tissue incompatibility reaction in only one patient (patient 11). The pattern of inflammatory reaction satisfied the postulated criteria for a tissue incompatibility reaction, i.e., opacification of the cornea was relatively homogeneous and neovascularization appeared to be directed exclusively toward donor tissue. This pattern is not compatible with descriptions of other authors of the "maladie du greffon,[28]" or the homograft reaction.[29] These workers defined the earliest stages of the reaction as a cellular destruction of the endothelium with progressive edema of the cornea leading to neovascularization. This difference in interpretation is probably due to the original selection of patients in whom the pattern of graft reaction was evaluated. The homograft reaction has customarily been described in patients with nonvascularized corneas. Following penetrating keratoplasty, a majority of the inflammation is of uveal origin. Our studies have been designed to eliminate all variables before attempting to define the tissue incompatibility reaction. Since using nylon suture, we have not experienced a graft failure in a patient with a nonvascularized cornea. The tissue incompatibility reaction that we have described is for vascularized corneas where the limbus serves as the origin for the reaction.

It seems likely that we would have encountered tissue incompatibility had we not used an intensive corticosteroid regimen. Perhaps the question concerning the importance of tissue incompatibility in leading to graft failure will be clarified when we are able to identify more cases which apparently demonstrate this mechanism.

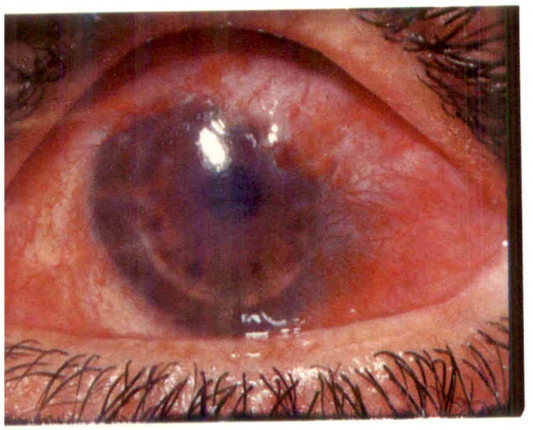
The systems of preoperative classification were designed as a measure of the degree of severity of structural change which was present in the cornea preoperatively. These severity gradients established only two morphologic signs as significant. These were: (1) neovascularization of the corneal stroma, and (2) evidence of intraocular inflammation. The latter parameter occurs only in the 1B+ and 4+ groups. The general severity gradient for vascularization is absent, superficial, and deep. Absent includes 0 and 1A+ stages, superficial is 2+, and deep is 3+ and 4+. Because vascularity was considered of principal importance when the two parameters were initially established, the possible history of intraocular structural change in the 1B+ group was overlooked and 1A and 1B were combined as a single category (cloudy cornea free of vascularization). However, subsequent studies indicated that prognosis for the 1B+ group was not as good as prognosis for the 1A or even 2+ group. This observation emphasizes the importance of previous intraocular disease. The 4+ category, the combination of severe corneal neovascularization and intraocular inflammation, is clearly the poorest prognostic group.

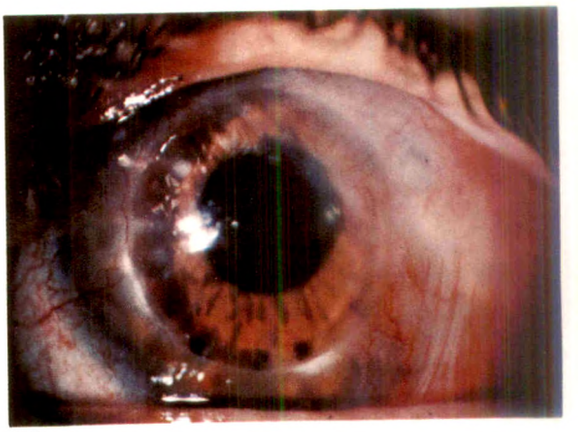
Reproducibility in patient classification was roughly tested by comparing the designations of each observer (the two authors). The 0+ and 1+ diagnoses were easily made and separated since one cornea was opacified and the other was free of opacity. The 1B+ was principally aphakic bullous keratopathy; in this case morphologic classification was aided by considering the patient's history. Separation between 2+ and 3+ was reasonably accurate since superficial neovascularization is easily distinguished from deep stromal vascularity. The separation between 3+ and 4+ was the most difficult. If corneal scarring and opacity were severe, the anterior chamber was frequently obscured. Similarly, if an anterior chamber reaction had become



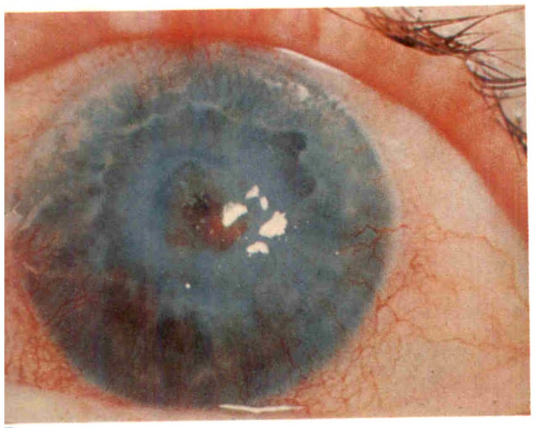


15B

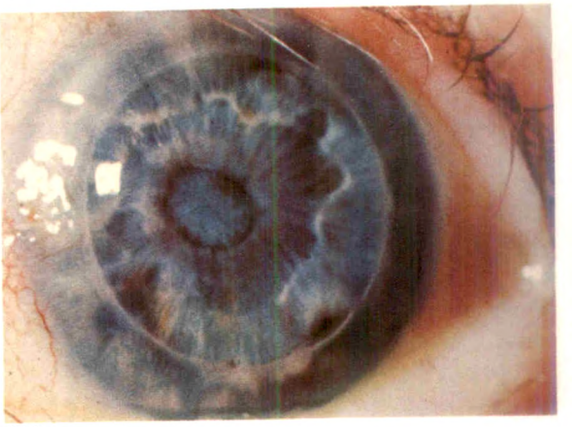




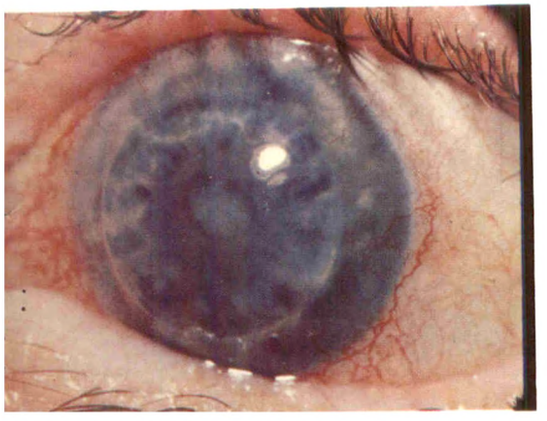
15D

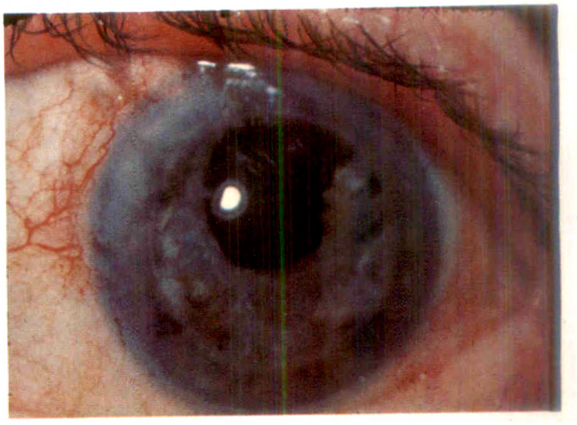


E



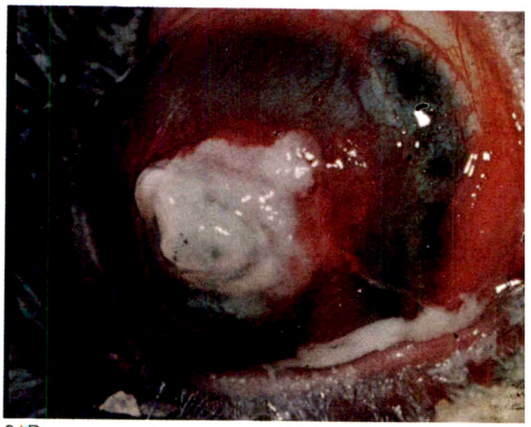
15F



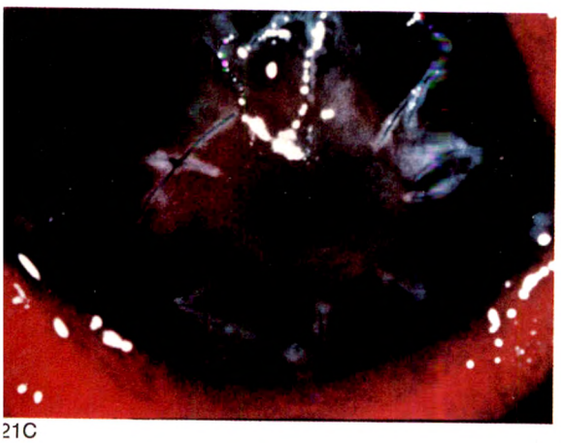




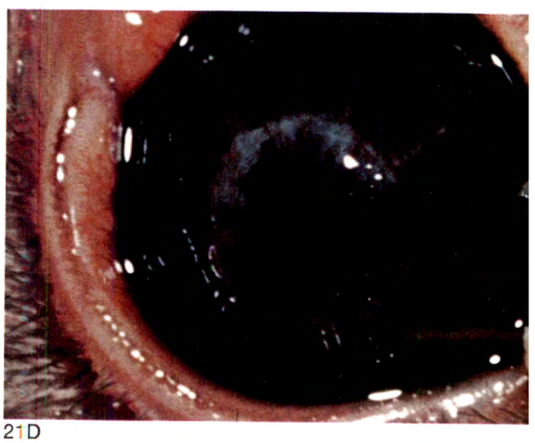
21A



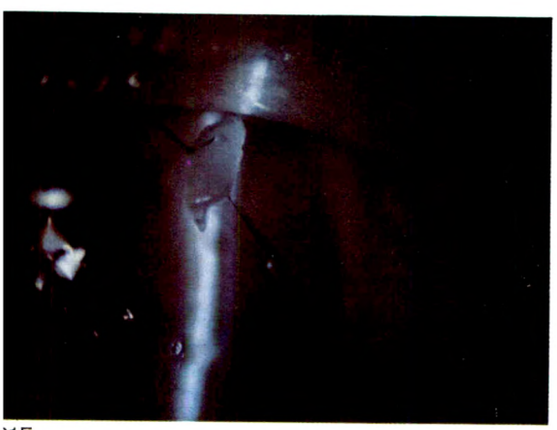
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21C



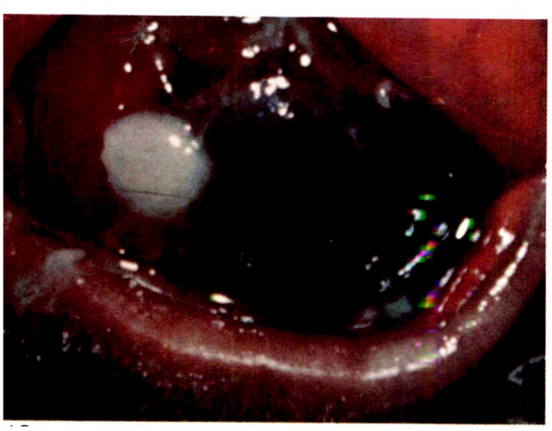
21D

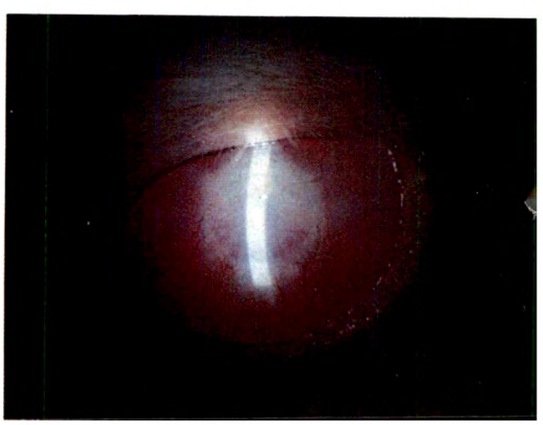


21E



21F





## DISCUSSION

Our general classification divides the delayed graft reaction into two general groups, (1) inflammatory and (2) mechanical. The mechanical failure group includes principally patients who were returned to surgery after keratoplasty for a subsequent procedure, most often a cataract extraction. Within this group we had a total of four cases, all resulting in failure. In each case, donor endothelium was mechanically traumatized, giving rise to an intractable bullous keratopathy. This may have resulted from either direct instrument contact with the endothelium or manipulation of the cornea during cataract delivery. It would appear to be a factor which can be controlled by improved surgical technique. In this series, there have been no delayed failures due to trauma during the past two and one-half years, even though a greater number of postkeratoplasty lens extractions were performed (11 lens extractions, 1967–69 vs seven, 1964–67). Mechanical failure is included in this dicussion for completeness. Technical refinements should eventually eliminate mechanical failures as a cause of the delayed graft reaction.

The inflammatory delayed reactions exemplify a syndrome which has frequently been interpreted as a delayed-onset allograft reaction. Case reports in the ophthalmic literature have often analogized this reaction to the second-set reaction.[1,2] An example is the reaction which occurs in an initially grafted eye, following subsequent keratoplasty on the patient's second eye.[3] The interpretation is that the patient, who had been immunized to allogeneic corneal tissue during the initial graft, develops an anamnestic response to the corneal donor button in the second eye. The antibody so produced reacts with the initial donor cornea. (In our 12 patients with bilateral surgery this reaction has not been seen.)

Characterization of the delayed graft reaction is somewhat vague.[4,5] Most authors emphasize that only the donor cornea is involved in the inflammatory reaction, based on the fact that it alone becomes opaque. Our experience differs somewhat. The course of the reaction we saw has already been described. We shall present the pathogenetic events in sequence. There are two clinical patterns of delayed reaction: the corneal pattern predominates, accounting for over 75% of reactions. The uveal pattern, though less frequent, can also lead to graft failure. In the corneal sequence, the initial, presenting lesion is a totally inflamed cornea (Fig. 5) in which inflammatory infiltrate occurs in both donor and host, and dormant ghost vessels of the host become markedly engorged. The pattern changes if the inflammation is allowed to proceed to graft failure. Inflammation still prevails in the donor and host, but the donor cornea now demonstrates predominantly edema, an indication that the inflammatory process has involved the endothelium. At this stage the reaction is difficult to reverse; the donor cornea subsequently progresses to bullous keratopathy. Once the inflammation has resolved, either spontaneously or following corticosteroid medication, the cornea demonstrates a classically de-

Fig. 21 (Moore and Aronson). Factors leading to early graft failure in rabbits. (A) Wound dehiscence eight days following surgery. (B) Same animal with prolapse of intraocular contents 35 days following surgery. (C) Silk suture toxicity 13 days after penetrating keratoplasty. (D) Graft failure secondary to silk suture toxicity, 60 days after surgery. (E) Nylon suture free of reaction 13 days after surgery. (F) Clear graft 60 days postsurgery in which interrupted nylon sutures were used. (G) Staph. aureus abscess in a suture tract, nine days after grafting. (H) A probable tissue incompatibility reaction (pigmented donor to albino host) in which other causes of graft failure had been eliminated.

scribed delayed graft reaction, i.e., an opaque donor cornea with clear surrounding host tissue.

The clinical course of the uveal pattern parallels the corneal picture, except that the degree of corneal and limbal inflammation is greatly reduced. In the early course of this disease, the patient demonstrates a rather severe anterior chamber reaction with approximately 2 to 3+ cells and flare. KP are noted on both the donor and inferior host endothelium. As the disease progresses, the donor cornea undergoes edematous changes which may lead to bullous keratopathy. Again, the classic picture of resolution is an opaque, bullous donor cornea with old KP on its endothelial surface and a clear host. Combined corneal and uveal patterns occur frequently with a predictable, relatively ominous outcome.

The pathogenetic sequence followed by the delayed graft reaction is initially that of a severe inflammation which can destroy parenchymal cells. Theoretically, the episode is always self-limited, so that if donor tissue can survive the reaction, a good result will follow spontaneously. However, the endothelial cells of the donor cornea appear to be much more vulnerable than those of the host; these cells must be protected from the ravages of the inflammatory response. Graft failure, a physiologic failure of the cornea produced by an inflammatory reaction, occurs when endothelial cells are destroyed.

Our experience supports the contention that treatment of delayed graft reactions should be successful if the patient is seen early in the course of his inflammatory reaction. If patients are seen within an adequate time of inflammatory onset, the reaction can be reversed. The most critical aspect in therapy is suppression of the inflammatory response without regard to the etiologic agent. In our protocol, patients are immediately started on topical corticosteroid. If epithelial edema is also detected, the patient receives simultaneous subconjunctival corticosteroid therapy until inflammatory signs resolve. Inflammatory signs can be reversed even in delayed graft failures, although endothelial damage may produce bullous keratopathy.

We have treated specific bacterial or viral (herpes simplex) diagnoses simultaneously with the anti-inflammatory regimen. Following specific evidence of etiology, specific antimicrobial therapy is started and continued until cultures are negative (bacterial) or corticosteroids are discontinued (herpes simplex). This combined therapy has been effective in controlling the specific agent, but rapid resolution of the inflammation by high-dosage corticosteroid must be emphasized as the critical therapeutic objective.

Identifiable exogenous stimuli played a significant role in delayed graft reactions. Of 42 cases with inflammatory delayed graft reactions, 32 were related causally to exogenous stimuli (Table 26). The prevalent cause of graft failure was pathogenic bacteria. Each of these patients presented long after functional changes of the donor cornea had occurred.

Several categories, e.g., indigenous bacteria and upper respiratory infection virus, are questionable in relation to a defined pathogenic agent. For example, indigenous bacteria comprised diphtheroids and Staph. epidermidis, which were demonstrated in abundance on culture and have been related to disease in the past.[6,7] Undoubtedly, such microbes take advantage of structurally altered ocular vascular permeability and produce an immunogenic reaction and consequent corneal inflammation.

The URI group is diagnosed by history. The patient either demonstrates signs of upper respiratory disease or relates a history of such experience. One patient with a long history of acute spondylitis and iritis in both eyes following upper respiratory infections experienced delayed graft reactions of the uveal type during two URI episodes. The pathogenetic agent in these reactions could have been introduced either exogenously or endogenously. In exogenous disease, the vi-

rus proliferates in the conjunctiva, producing a conjunctivitis. In the structurally altered graft eye, this leads to engorgement of blood vessels in the host cornea, which increases the amount of antiviral antibody in both the donor and host corneas. Combined viral antigen and antibody produce an immunogenic inflammatory reaction. Experimentally, in eyes where the uveal structure has been altered, this immunogenic reaction may present as a uveitis. In the endogenous reaction, antigen-antibody complexes precipitate out in the uvea and provoke an immunogenic uveitis.[9,10] In this instance, the enhanced uveal vascular permeability produced by previous uveitis sufficiently increases ocular blood flow to allow systemic antigen-antibody complexes to enter the eye in adequate concentration to produce an inflammatory response.

The possibility that these reactions represent late tissue incompatibility reactions should be considered. None of the six idiopathic cases demonstrated an inflammatory stimulus, yet all showed delayed reactions, three of which proceeded to graft failure. Each of these cases demonstrated extremely heavy vascularization of the host cornea (four chemical keratitises), a circumstance which should theoretically favor a tissue incompatibility reaction.

In general terms, if tissue incompatibility were to play a role in the graft reaction, it should be during the early graft period. Those antigens which are most accessible to the host immune system—that is, the soluble antigens—should disappear rapidly in this early period. Disappearance of these antigens has been demonstrated in heterologous renal grafts and skin homografts.[11,12] It can be assumed that the donor cornea is free of soluble antigenicity in the delayed graft period. (As already noted, this type of reaction in our series has been suppressed by the corticosteroid therapy.)

In the delayed graft period, fixed antigens must be the source for antigenicity of the donor cornea, i.e., relatively insoluble antigenic loci. Such antigens probably are immunochemically related to the soluble antigens of the cornea and can cross-react with antibody to soluble antigen. Antibody or immune competent cells must now come to the donor cornea to react with the fixed antigen contained within the donor graft. This means that a second stimulus must initiate the inflammatory reaction which secondarily activates the tissue noncompatibility reaction. In theory, the experimental second-set reaction produces an anticorneal antibody which will react with donor corneal tissue. In order to gain access to fixed antigenicity, the antibody must be humoral in a clear donor cornea.

Four of the idiopathic cases have demonstrated almost continuous inflammatory reactivity throughout the course of their graft history and have required almost continuous corticosteroid therapy. Each of these cases demonstrated severe vascularization of the host cornea and may represent an example of a delayed tissue incompatibility reaction.

The other examples of delayed graft reaction have almost always demonstrated the presence of a second stimulus, e.g., exogenous microbes. We believe that these stimuli produce the inflammatory reaction which leads to delayed graft failure. However, it is possible that such exogenous reactions can ignite a tissue incompatibility reaction which in turn leads to graft failure. Differentiation of this reaction into such components is an extremely difficulty undertaking.

The significance of host responsivity was determined by a series of immunologic tests. The overall pattern in the delayed graft reaction group indicates a relatively normal distribution curve for all values tested. It is particularly interesting to note that all patients fell within two standard deviations of the normal range for all tests. The immune distribution curve was unusually tight for this population, indicating that an individual must be able to produce an adequate immune response if a delayed graft reaction is to occur.

Altered structure emerges as the most significant single variable studied in this series (Tables 27 and 28). In general, the highly vascularized host cornea or the uvea which had experienced previous inflammation apparently predisposed to a delayed graft reaction. No graft which demonstrated a delayed reaction was free of a moderate amount of structural change. The substantial correlation between pre- and postoperative corneal structural change is hardly surprising; obviously, the cornea which has once demonstrated neovascularization will demonstrate this change in the postoperative period.

The dynamic pathway by which structural change predisposes to recurrent inflammation merits comment. In rabbit corneal graft experiments,[8] grafts were allowed to subside for three months postoperatively. At the end of this period, a severity gradient of corneal structural change was established. Corneal change was classified as mild, moderate, and severe: (1) mild—only ghost vessels in the host, (2) moderate—active vessels in the host, and (3) severe—active vessels in both the host and donor. A normal cornea was one in which no surgery had been performed. Radiotagged HSA($^{131}$I) or HGG ($^{125}$I) was administered intravenously and allowed to equilibrate—the corneas were then counted for accumulated plasma. All the donors were appreciably above the normal. The moderately changed host cornea, which compares most accurately to the human cornea undergoing a delayed graft reaction, showed a marked increase in ocular vascular permeability compared with the mildly changed cornea. Subsequently, rabbits were immunized and topically challenged with several antigens. The same criteria for corneal classification were applied. The moderately reacting host corneas showed severe inflammatory reactions and progressed to delayed graft failure. The animals with mildly reacting corneas showed much less severe reactions; none progressed to graft failure.

These experiments demonstrate the interplay between exogenous stimulus and structural alteration. The vascular changes in the host cornea increase corneal vascular permeability. On challenge with a topical antigen, as in the topical immune model, an immunogenic delayed graft reaction is produced.

The role of socioeconomic factors (patient failure) in predisposing to delayed graft reaction and delayed graft failure is probably a secondary operative variable. The lowest socioeconomic group, the indigent SFGH patients, demonstrated the highest incidence of delayed graft reactions and also the highest incidence of delayed graft failure (Table 29). To avoid speculation (which may be extremely important), evaluation has been limited to quantitative factors. Of the 15 SFGH patients with delayed graft reactions, nine were known alcoholics. Few UC or private patients with reactions had a documented history of alcoholism. The sustained physiopathologic effect of alcohol on blood vessels in the host cornea leads to a prolonged vasodilation. Such a reaction has been well described. In this "morning after" response, the individual demonstrates vasodilation of conjunctival vessels—"bloodshot" eyes. Undoubtedly, such vasodilatation leads to enhanced vascular permeability, which in turn intensifies the host response to exogenous stimuli. Of the cases mentioned, five patients demonstrated bacteria in both conjunctival sacs, but only the graft eye showed corneal inflammation.

As noted earlier, the incidence of delayed graft failure is directly related to the delay in time of presentation of patients after the onset of symptoms. The percentage of graft failures during the early period was not appreciably different in the three series (Table 15). However, when patients were left to their own recognizance, graft failure occurred frequently in SFGH patients. The SFGH patients were extremely tardy in appearing for treatment following the onset of a delayed graft reaction.

When delayed graft failure occurred in

the private series, an extenuating circumstance could usually be identified, such as the failure to recognize a graft reaction in her blind eye by patient 13.

Undoubtedly, factors other than socioeconomic played a role in this predisposition toward delayed graft reaction, but such an evaluation is beyond the scope of this paper.[13]

Summarizing our discussion on the early graft reaction, we described our ideal protocol for corneal graft management during the early graft period. In theory, once sutures have been removed, the grafted eye should rapidly reach a homeostasis and remain free of active inflammation. In our ideal graft, there is only minimal structural change in the host cornea (as well as the donor), the patient is free of symptoms, and no longer requires therapy.

During long-term management of grafts, our principal goal is prophylactic: to prevent delayed graft reactions. As noted, delayed graft reactions can be predicted with some degree of accuracy by evaluating the structural status of the host cornea once it has stabilized. On this basis, patients with relatively severe structural changes are seen at closer intervals than those with minimal host vascularization. As a general rule, we attempt to see patients at monthly intervals (following suture removal) between the third and the sixth month, at trimonthly intervals between six and 18 months, and at semiannual intervals thereafter. If there is evidence of progressive structural change, they are started on a short course of corticosteroids (two to three weeks). This includes Prednefrin Forte 1% hourly between six A.M. and 10 P.M., plus a specific antimicrobial daily if indicated. As active inflammation resolves, corticosteroids are rapidly reduced, then discontinued. During active therapy, the patient is seen one to three times a week. After medication is withdrawn, the patient is followed according to the described schedule.

A small group of patients have required continuous corticosteroid therapy following keratoplasty. Dosage ranges from once a day to one drop weekly. If corticosteroid is discontinued, these patients develop inflammatory reactivity within several days. This group of patients is followed at weekly to monthly intervals to ensure that no complications have occurred. Naturally, maximal therapy is resumed should inflammation exacerbate.

Finally, it is possible for structural alteration to modify with the passage of time. For example, a patient with herpes keratitis experienced two delayed graft reactions within the first 18 months of grafting, but the eye has been completely quiet for the past two years, demonstrating marked attenuation of vessels in the host cornea. At present, we still consider such an individual to be a potential reactor. In general, all patients who have had penetrating keratoplasty have some degree of altered structure. Such patients must be impressed with the possibility that they may have a delayed reaction in the future and, to avoid delayed graft failure, they should alert us immediately to (1) blurred vision or (2) redness or pain in their eyes. If the patient is a referral from a distance, we ask the referring ophthalmologist to keep us advised of the onset and progression of the delayed graft reaction. We emphasize that any uncertainty necessitates sending the patient to us for therapy. This rigid follow-up regimen is designed to avoid delayed graft failures.

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## LONG-TERM RESULTS IN MAN

A long-term graft success is defined as a corneal graft which has remained clear for nine months or longer. The longest period of follow-up in this series is just under five years, but the total long-term series is comprised of 146 cases, 129 eyes, and 121 patients (Table 30). This represents more than 95% of all patients who were operated upon; only six patients were lost to follow-up.

Long-term success was usually designated on the basis of personal observation of the patient by one of us in order to validate that the graft had remained clear. An alternative to this procedure for patients who could not return to San Francisco for long-term evaluation was a photograph (preferably slit lamp) of the clear donor button and a record of the patient's final visual acuity. Long-term failures included any cornea which became clouded or opaque.

Variables evaluated on a long-term basis included the preoperative morphologic, etiologic, and immunologic classifying criteria. Other evaluations were the degree of success achieved in regard to visual acuity; the occurrence of ocular complications, whether or not they were cornea-related; long-term effects of suture toxicity; and long-term effects of socioeconomic status on graft results.

The overall distribution of graft failures showed a definitely higher rate in the first three months, or early graft period (Fig. 17). Twenty-one of 40 failures (52.5%) occurred during this early period. The incidence of failure diminished with time. Thirteen of 19 (68%) delayed graft failures occurred between three months and one year. Only six grafts failed after the first year.

Preoperative classifying criteria have been extended to the long-term series.

Morphologic evaluation (Table 30) revealed overall success of $> 72\%$ in all cases. Broken down into subgroups, success rates were as follows: 1A and 2+: 100%, 0+: $> 96\%$, 1B+ : 71%, and 3 to 4+ : just over 60%. It is interesting to note that when cases with poor prognosis were divided into primary and multiple graft groups (Table 31), no appreciable difference in long-term success could be noted. Success improves markedly when evaluated by eyes: overall: 81%, 1B+: 100%, 3+: 69%, and 4+: 73%, respectively. Results are approximately the same for patient evaluation.

By etiologic classification, 100% success was achieved in all cases of keratoconus, familial corneal dystrophy, corneal trauma, and herpes zoster keratitis (Table 32); aphakic bullous cases: 79% success, which when corrected for eye and patient, improved to 95%;

TABLE 30

LONG-TERM KERATOPLASTY RESULTS BY MORPHOLOGIC CLASSIFICATION

| Classification | Total Cases | Successful Grafts | | Total Eyes | Successful Grafts | | Total Patients | Successful Grafts | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | | No. | % | | No. | % |
| 0+ | 26 | 25 | 96 | 26 | 25 | 96 | 20 | 19 | 95 |
| 1A+ | 1 | 1 | 100 | 1 | 1 | 100 | 1 | 1 | 100 |
| 1B+ | 14 | 10 | 71 | 10 | 10 | 100 | 10 | 10 | 100 |
| 2+* | 12 | 12 | 100 | 12 | 12 | 100 | 12 | 12 | 100 |
| 3+* | 32 | 20 | 62 | 29 | 20 | 69 | 28 | 20 | 71 |
| 4+*† | 61 | 38 | 62 | 51 | 37 | 73 | 50 | 36 | 72 |
| Total | 146 | 106 | 72+ | 129 | 105* | 81 | 121 | 98 | 81 |

* This includes 29 regrafted eyes, of which 21 (72%) have had successful results.

† Thirteen eyes had perforated prior to keratoplasty; eight (62%) have had successful results.

herpes simplex: 62% for cases and 72% for eyes and patients. This percentage was extremely close to idiopathic stromal keratitis, where 68% of cases and 75% of eyes and patients were successful. Bacterial ulcers and other diagnoses, both small series, demonstrated over 80% success for eyes and patients. The poorest results were in the physical or chemical agent category. Only 38% of cases were successful, a figure which remained unchanged for eyes and patients.

Immunologic evaluation for the overall series would indicate no significant difference for any of the tests evaluated (Table 33). Parameters that were useful in the early graft period were not pertinent during the delayed graft period. Added together, overall significance was lost.

The overall functional results are expressed in Table 34. Degree of success is described as symptomatic relief, some visual improvement. such as visual acuity of 20/40. Almost every patient demonstrated symptomatic improvement—for example, a perforated cornea was reconstituted and the eye was saved. More than 54% of all grafted eyes attained a visual acuity of > 20/40. On the basis of preoperative morphologic classification, the best visual results were obtained in the good prognosis categories (76%). However, a reasonably significant percentage of eyes in the poor prognosis categories (41%) also attained visual acuity of > 20/40.

As already noted, complications are divided into two general categories, those related to the penetrating keratoplasty—for example, secondary glaucoma—and those not related to the graft but occurring in eyes with corneal disease. Significant complications which have persisted as long-term ocular problems are listed in Table 18. Glau-

TABLE 31

LONG-TERM KERATOPLASTY RESULTS: PRIMARY VS MULTIPLE SURGERY

| Morphologic Classification | Total Cases | Successful Grafts | % Success |
|---|---|---|---|
| Primary grafts | | | |
| 3+ | 22 | 14 | 64 |
| 4+ | 38 | 23 | 61 |
| Total | 60 | 37 | 62 |
| Multiple grafts | | | |
| 3+ | 10 | 6 | 60 |
| 4+ | 23 | 15 | 65 |
| Total | 33 | 21 | 64 |

TABLE 32

LONG-TERM KERATOPLASTY RESULTS: ETIOLOGIC CLASSIFICATION

| Etiology | Total Cases | Successful Grafts | | Total Eyes | Successful Grafts | | Total Patients | Successful Grafts | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | % | | No. | % | | No. | % |
| Keratoconus | 12 | 12 | 100 | 12 | 12 | 100 | 10 | 10 | 100 |
| Corneal dystrophy | 14 | 14 | 100 | 14 | 14 | 100 | 9 | 9 | 100 |
| Aphakic bullous | 26 | 21 | 81 | 22 | 21 | 95 | 22 | 21 | 96 |
| Trauma | 6 | 6 | 100 | 6 | 6 | 100 | 6 | 6 | 100 |
| Herpes simplex | 34 | 21 | 62 | 29 | 21 | 72 | 29 | 21 | 72 |
| Herpes zoster | 5 | 5 | 100 | 5 | 5 | 100 | 5 | 5 | 100 |
| Bacterial keratitis | 6 | 4 | 66 | 5 | 4 | 80 | 5 | 4 | 80 |
| Idiopathic stromal keratitis | 22 | 15 | 68 | 20 | 15 | 75 | 20 | 15 | 75 |
| Physical or chemical agent | 13 | 5 | 38 | 10 | 4 | 40 | 10 | 4 | 40 |
| Other diagnoses | 8 | 3 | 39 | 6 | 3 | 50 | 5 | 3 | 60 |
| Total | 146 | 106 | 73+ | 129 | 105* | 81 | 121 | 98 | 81 |

* This includes 29 regrafted eyes of which 21 (72%) have had successful results.

TABLE 33

IMMUNOLOGIC EVALUATION OF LONG-TERM GRAFT RESULTS

| Diagnostic Category | Outcome | Total Cases | IgA | IgM | IgG | Early IgG |
|---|---|---|---|---|---|---|
| 0+ | Success | 14 | 267 | 98 | 1063 | 6.8 |
| | Failure | 2 | 185 | 127 | 1479 | 8.0 |
| 1A+ | Success | 1 | 301 | 28 | 1032 | 7.5 |
| | Failure | | | | | |
| 1B+ | Success | 9 | 215 | 156 | 1119 | 7.1 |
| | Failure | 4 | 289 | 102 | 1177 | 7.2 |
| 2+ | Success | 11 | 270 | 87 | 1034 | 7.5 |
| | Failure | | | | | |
| 3+ | Success | 17 | 279 | 111 | 1199 | 7.2 |
| | Failure | 14 | 253 | 117 | 1128 | 7.4 |
| 4+ | Success | 42 | 235 | 149 | 1289 | 8.3 |
| | Failure | 20 | 213 | 136 | 1188 | 7.0 |
| Total success | | 94 | 251 | 127 | 1243 | 7.7 |
| Total failure | | 40 | 234 | 126 | 1180 | 7.2 |

coma was the most frequent single complication, occurring in 13% of eyes. Other complications were less frequently seen and were relatively evenly divided. It is especially interesting to note that only five eyes (3.5%) showed long-term deterioration, intractable glaucoma, or phthisis bulbi, three finally requiring enucleation. These complications occurred most frequently in the poor prognosis categories (Table 35). As best we can determine, a vast majority of these complications were unrelated to corneal surgery, but reflect intraocular involvement simultaneous with the corneal disease process.

Long-term comparison of silk and nylon suture cases may be premature at this time because only 55 nylon cases have been followed for one year or longer. However, at

TABLE 34

LONG-TERM FUNCTIONAL RESULTS FOLLOWING KERATOPLASTY

| Morphologic Group | Total Eyes | Some Visual Improvement | Visual Acuity >20/200 | Visual Acuity >20/40 | |
|---|---|---|---|---|---|
| | | | | No. | % |
| 0+ | 26 | 1 | 2 | 22 | 85 |
| 1A | 1 | | | 1 | 100 |
| 1B | 10 | 1 | 1 | 7 | 70 |
| 2+ | 12 | 2 | 3 | 7 | 58 |
| Total | 49 | 4 | 6 | 37 | 76 |
| 3+ | 29 | 4 | 3 | 11 | 38 |
| 4+ | 51 | 4 | 8 | 22 | 43 |
| Total | 80 | 8 | 11 | 33 | 41 |
| Grand total | 129 | 12 | 17 | 70 | 54 |

TABLE 35

OCCURRENCE OF NONCORNEAL OCULAR COMPLICATIONS BY MORPHOLOGIC CLASSIFICATION

| Morphologic Classification | Total Eyes | Complications | |
|---|---|---|---|
| | | No. | % |
| 0 | 26 | 4 | 15 |
| 1A+ | 1 | 0 | 0 |
| 1+ | 10 | 3 | 30 |
| 2+ | 12 | 3 | 25 |
| 3+ | 29 | 11 | 38 |
| 4+ | 51 | 26 | 51 |
| Total | 129 | 47 | 36 |

TABLE 36

COMPARISON OF LONG-TERM RESULTS WITH SILK AND NYLON SUTURES

| Morphologic Classification | Total Cases | Successful Grafts | |
|---|---|---|---|
| | | No. | % |
| 8-0 virgin silk suture | | | |
| Better prognosis | 37 | 32 | 86 |
| Poorer prognosis | 54 | 31* | 57 |
| Total | 91 | 63 | 69 |
| 10-0 Ethilon suture | | | |
| Better prognosis | 71 | 17 | 100 |
| Poorer prognosis | 38 | 32 | 84 |
| Total | 55 | 49 | 89 |

* The six delayed graft failures which occurred after 12 months have been counted as successful cases so that both series have been measured for an equal time interval.

TABLE 37

EVALUATION OF LONG-TERM RESULTS BY SOCIOECONOMIC CRITERIA

| Patient Series | Total Cases | Prognosis | | Successful Graft | |
|---|---|---|---|---|---|
| | | Good | Poor | No. | % |
| Private | 92 | 29 | 63 | 68* | 74 |
| UC | 34 | 22 | 12 | 28* | 82 |
| SFGH | 20 | 2 | 18 | 10* | 50 |
| Total | 146 | 53 | 93 | 106 | 73 |

* Includes one case of graft failure secondary to subsequent surgery in each group.

the present time, only three delayed graft failures have occurred in nylon suture cases. Comparative long-term results for silk and nylon suture reveal a dramatic difference in overall success rate, 89 nylon vs 69% silk (Table 36), when cases have been comparably followed for the first year after surgery.

The final factor which should be considered in long-term results is the overall effect of socioeconomic factors on success. The incredibly high incidence of delayed graft reactions in the indigent group (SFGH) prompted us to chart long-term success rates in each patient series (Table 37). The long-term success rate for SFGH cases is 50%, as compared to 74% for private patients, and 82% for UC cases.

## DISCUSSION

Evaluation of long-term graft results should focus on accumulating data which will permit accurate preoperative prognosis. One inherent drawback to such data is the heterogeneity in time for the series. It may take a single center five to 10 years to accumulate sufficient data for a significant prospective series.

The long-term data within this report manifest the usual shortcomings of a single-center project—that is, a lack of homogeneity of the series since a majority of patients have been followed for a much shorter time interval than the longest period reported. These data merit presentation, however, because they demonstrate changes in the rate of success which occur over prolonged time intervals related to control of graft variables. We should emphasize that many larger series have been reported in which patients have been followed for a longer period of time,[1-3] but these series frequently included lamellar keratoplasty.

The criteria which we have considered over the long term include: (1) temporal occurrence of graft failure after the early graft period; the incidence of failed grafts in (2) morphologic, (3) etiologic, and (4) immunologic groups; functional aspects of long-term grafted eyes, including (5) visual acuity and (6) incidence of noncorneal complications; and finally, the effect of (7) suture and (8) socioeconomic factors were evaluated.

The distribution of graft failure with time is presented in Figure 17. A majority of cases fail in the early graft period. The number of subsequent failures appears to diminish with the passage of time. The reason for this change in rate of failure probably represents normalization of enhanced ocular vascular permeability (OVP) with time. During the early graft period a number of inflammogenic variables are operative which produce a marked increase in OVP, indicated by the redness of the eye during this period. As time passes, OVP normalizes and the rate of delayed graft reactions and failures diminishes. This is particularly evident in the patient who experienced two delayed graft reactions within the first 18 months, but has been free of recurrent inflammation for the past two years, although he was presumably exposed to the same stimuli. Apparently, neovascularized channels tend to become inactive with time, allowing OVP to return to normal, after which predisposition toward recurrent inflammation diminishes considerably.

Other factors undoubtedly play secondary roles in inflammatory recurrence. A patient is usually exposed to a stimulating agent, as in the case of Staph. aureus and herpes simplex, the patient apparently is chronically infected with the agent. (However, in this series herpes reinfection of the cornea after grafting occurred infrequently). Obviously, the degree of host response also plays a role, since no individuals below the series mean demonstrated a reaction during the delayed period. Similarly, individuals within the indigent socioeconomic class showed a predisposition to delayed reactions and failure. Each of these variables must play a role in producing inflammatory recurrence; however, they would seem to be subordinate to OVP, as expressed through structural alteration.[4]

The evaluation of long-term surgical results by preoperative classifying criteria yielded results similar to those for the early graft period. As in the early graft period, the morphologic classification was the most pertinent. Cases with poor prognosis (3 and 4+) demonstrated much poorer long-term success than those with good prognosis. This was also true for eyes. It is particularly interesting that a majority of delayed graft failures as well as early graft failures occurred in the 3+ and 4+ groups, so that long-term prognosis for these cases was decidedly worse than early results (62 vs 82%).

Results were similar in the etiologic classification system. The cases with poor progno-

sis in the etiologic classifications of chemical and physical agents, herpes simplex, and idiopathic stromal keratitis, demonstrated a higher incidence of delayed graft failure than did those with good prognoses. Once again, this was markedly improved for eyes over cases. (As already noted, the similarity between morphologic and etiologic results probably stems from the considerable overlap of the two classifying sytems.)

Preoperative immunologic classification proved to be much more meaningful in the early graft period than in the delayed graft period. Early IgG evaluation was significant in predicting graft success during the early period; however, when applied to long-term results, it did not offer prognostic utility. The reason for this loss of prognostic relevance has been partially analyzed in this discussion. It is probably related to the effect of increased OVP on the level of host inflammatory response to a given stimulus. The acute or early graft reaction represents a relatively high level of inflammatory reactivity to a stimulus which is present for a reasonably long interval. The individual who is prone to inflammation, as identified by early IgG estimation, demonstrates this proclivity for graft failure. The delayed graft reaction is a relatively short inflammatory episode in which graft failure occurs when donor endothelium has decompensated. Since the patient is not being actively treated at the time of onset, the reaction can progress to failure before treatment is instituted. It seems likely that the immunologic testing procedures are not sufficiently sensitive to prognosticate the potential reaction.

The roles of suture and socioeconomic status were evaluated because they appear to have substantial influence on long-term graft results. The suture toxicity in the long-term period may be explained by the severity of the graft reaction during the early graft period. In general, in the early graft period silk-sutured cases demonstrated more severe structural alterations than nylon-sutured cases. This observation is compatible with the demonstrated toxicity of silk suture and the markedly greater number of silk-sutured graft failures in the early period. Evidently, a certain number of cases which succeeded in the early period incurred sufficiently severe structural change to predispose them to a delayed graft reaction.

The role of socioeconomic factors in predisposing to delayed graft failure was clarified by studies of the indigent patients (SFGH), who showed an extremely high rate of failure. This observation is particularly interesting because early graft failure rates in the indigent group were virtually identical with the private and UC clinic (fixed or minimal fee) groups. On his own recognizance, the indigent patient showed virtually no concern for the care and outcome of his graft. This is evidenced by (1) the high incidence of external disease in these patients' eyes after grafting, and (2) the prolonged delay in presenting for treatment displayed by these patients despite their awareness of active ocular disease.

The inordinately high rate of delayed graft failure in this group compelled us to evaluate whether keratoplasty is justified in such a group of individuals. Although penetrating keratoplasty is an excellent therapeutic measure in a responsible individual, it represents a liability to the patient who pays no attention to protecting it. In the last analysis, such a patient is better served by a treatment which requires no patient cooperation; this usually means a conjunctival flap or, in other words, no positive effort to restore vision.

The last point of discussion will be the functional quality of the grafted eye. Overall, the corneal graft appears to offer an excellent functional prognosis. Our results (Table 34), as those of others, would indicate that in a high percentage of grafted patients excellent visual acuity ($> 20/40$) will be achieved. In cases with good prognosis, the rate of excellent visual acuity is better than 75%. Even in cases with poor prognosis, in a meaningful percentage (41%) this

level of visual acuity is achieved. The reason for this is that corneal disease cases are frequently free of other intraocular complications (Tables 18 and 35). When a complication does occur, it is usually in the anterior eye (glaucoma) and responds favorably to medical or surgical control. Altogether, only 20 eyes demonstrated intractable or incurable posterior ocular diseases such as senile macular degeneration or optic atrophy. In some cases, e.g., those with retinal detachment, excellent results were achieved following retinal surgery; in other cases—those with optic atrophy secondary to glaucoma, for example—good results would have been achieved except for the fact that there was pre-existing damage.

In general, long-term results show a decline in the rate of graft failures with time as with most surgical procedures. Two of the principal causes of delayed graft failure—suture toxicity and socioeconomic predilection—can be rectified. If this transpires, long-term graft results should reach the level of results in the early graft period.

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## STATISTICAL EVALUATION

The data on penetrating keratoplasties sutured with 8-0 virgin silk and 10-0 Ethilon were analyzed by discriminant function. Details of the coding are given in Table 38. Linear discriminant analysis (as used in this study) is a mathematical method of assigning a case to one of two outcome categories on the basis of various characteristics. Categories are computed from data where the outcome is known, in order to evaluate the importance of the various characteristics in the outcome or to predict the outcome of future similar cases. In this study, the outcome under evaluation was success or failure of the transplant; early and late outcomes were evaluated separately. The other characteristics are listed in Table 38.

Discriminant analysis is based on the fact that the mean values of each characteristic are likely to differ between the two outcome groups. Analyzing the characteristics compositely, their predictive ability may be stronger than any one alone would be. The linear discriminant equation is of the form:

$$Z = a_1 x_1 + a_2 x_2 + \ldots + a_2 x_1$$

where each $x_1$ is one of the discriminating characteristics and each $a_1$ is a constant. The $a_1$ categories are selected in such a way as to maximize the difference in Z values for cases in the two groups. For each case, a Z value is computed from the x values for that case and the constant a values. If the function worked ideally, there would be no overlap in the Z values for the cases in the two groups. For example, all Z values in the first group might be between 5 to 10, while all values for the second group might be between 20 and 29 (Fig. 18).

The initial study on corneal transplants su-

TABLE 38

VARIABLES AND CODES USED IN DETERMINING DISCRIMINANT FUNCTION

1. Etiological classification codes. It was planned to evaluate these 12 diagnostic categories with separate discriminant functions, but there were not enough cases of any one type.
2. Morphologic classification, coded 0 through 4.
3. Microbial pathogen. "None" coded 0, an entry coded 1.
4. Surgery procedure
   - Simple keratoplasty (1)
   - Keratoplasty combined with cataract extraction (2)
   - Keratoplasty+anterior chamber revision (3)

5–8. IgA, IgM, IgG, early IgG. Numbers as recorded.

9–10. Early and late outcome
   - Failure (0)
   - Success (1)

11–15. Wound, glaucoma, retinal detachment, secondary membrane, unrelated variables
   - No entry (0)
   - Check mark or entry (1)

16. Surgeon
   - TEM, Jr. (0)
   - Resident (1)

17. Combination code for morphologic classification and early IgG

| Morphologic Classification | Early IgG | Variable 17 |
|---|---|---|
| 0, 1, 2 | Anything | 0 |
| 3 | ≥8.1 | 0 |
| 4 | ≥9.1 | 0 |
| 3 | <8.1 | 1 |
| 4 | <9.1 | 1 |

18. Type of suture
   - 8-0 virgin silk (0)
   - 10-0 Ethilon (1)

## THE LINEAR DISCRIMINANT EQUATION

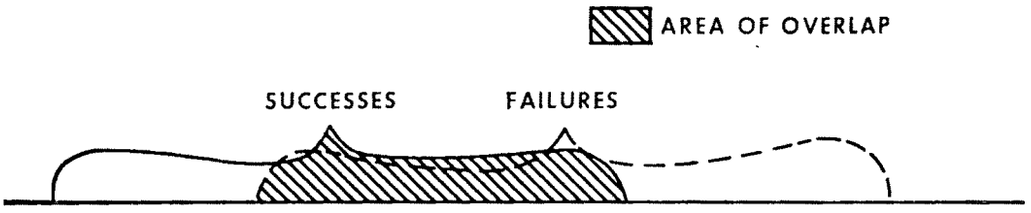



Fig. 18 (Moore and Aronson). Discriminant function analysis.

tured with 8-0 virgin silk was evaluated for early and late outcome (Table 22). Only cases in which outcome data were available have been included in this study. (Where other characteristics were unknown, mean values were used as estimates.) A second study has been made on all suture cases and this study has been evaluated similarly (Table 23).

The characteristics which contributed strongly to prediction in silk-sutured cases were morphologic classification and the wound. Other significant variables included secondary membrane formation and early IgG in early results (Table 23). Significant characteristics in silk-plus-nylon sutured cases included morphologic classification, the wound, secondary membrane formation, and the type of suture used, that is, silk or nylon. Unrelated variables appeared to be significant in late outcome cases (Table 22).

The discriminant function was statistically significant at $p \leq 0.01$ for all groups—that is, the separation in the Z values for the two groups is greater than would be expected purely by chance (Table 39). Translated into percent of failures which have been misclassified, approximately 25% of failures have been missed for early outcome and 20% for late outcome. The reverse of this—that is, success misclassified as failure—has occurred much less often.

TABLE 39

CASES MISCLASSIFIED BY DISCRIMINANT FUNCTIONS

| | All Sutures | | | | Silk Sutures Only | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | | Known Early IgG | | Total | | Known Early IgG | |
| | Early Outcome | Late Outcome | Early Outcome | Late Outcome | Early Outcome | Late Outcome | Early Outcome | Late Outcome |
| Number of Failures | 21 | 40 | 21 | 38 | 18 | 33 | 18 | 33 |
| Successes | 142 | 106 | 125 | 95 | 77 | 59 | 71 | 53 |
| Critical value* | 0 | +0.005 | 0 | +0.005 | −0.015 | −0.012 | −0.015 | −0.011 |
| Number of Failures misclassified as successes | 5 | 11 | 5 | 11 | 6 | 6 | 4 | 6 |
| Successes misclassified as failures | 13 | 23 | 13 | 17 | 5 | 9 | 7 | 9 |
| Percent of failures misclassified as success | 24 | 28 | 24 | 29 | 33 | 18 | 22 | 18 |

* Cases with Z values above this point would be classified as failures, below this point as successes.

## METHODS

Experimental studies in the rabbit were designed to evaluate both the early and the delayed graft reaction, as in the patient series. The significant variables in the early graft period are: (1) the surgical procedure, (2) the suture, (3) the exogenous microbial environment, and (4) tissue incompatibility reactions. Since tissue was taken immediately from young donor animals, primary donor failure did not occur. Experiments were designed so that each variable could be studied separately, then related subsequently to the other variables.

A delayed graft reaction has been defined as an inflammatory reaction involving the donor graft which occurs after the 75th postoperative day. The delayed graft reaction in the rabbit, as the reaction in man, appears to be principally related to exogenous stimuli, i.e., infection by a pathogenic bacterium. To evaluate further the role of exogenous stimuli in producting delayed graft reactions, a group of successfully grafted animals was topically challenged with immunogenic stimuli and experimental delayed reactions were produced.

The subsequent report describes the early graft reaction and the spontaneous and experimental delayed graft reaction in rabbits.

*Selection of animals*—Rabbits were selected from two breeding strains. The first, designated Horton's New Zealand White, was composed of a closed population of New Zealand White animals started in 1957 as 400 breeding pairs; no outside breeding stock was added thereafter. These animals, designated herein as albinos, were operated on when they weighed between 2500 and 3000 g. The second group, or Horton's Dutch, was purchased from a show farm and started as 200 breeding pairs in 1958. Since then, outside breeders have been added periodically, but these additions have been limited to pigmented rabbits that have characteristic "Dutch" traits, such as similar coat markings and dark eye pigmentation. These animals will be referred to as pigmented. They were operated on between 1500 and 2000 g in weight.

The total number of animals used in these experiments was considerable, probably numbering more than 350 animals. They were divided into seven experimental recipient groups as outlined in Table 40.

*Selection of donor grafts (allografts)*—The donor rabbit, whether albino or pigmented, was killed immediately before surgery. We attempted to use a single donor for two recipient allografts. No longer than two hours elapsed before the corneas were used. Donor corneas were selected from eyes free of corneal disease as determined by microscopic examination.

*Autografts*—Rotational autografts (180°) were performed on the second eye of each animal to serve as tissue histocompatibility control.

*The surgical procedure*—The first 100 animals were anesthetized with pentobarbital (about 15 mg/kg for induction). Since each animal underwent two surgical procedures, an indwelling venous catheter was used to facilitate periodic injection of anesthesia. Despite this precaution, more than 25% of the animals died in the immediate postoperative period. A gas inhalant (Metafane) was adopted for anesthetizing the remaining animals in a closed gas recycling system, so that the depth of anesthesia could be better controlled than it had been with pentobarbital. Refinement of the inhalation technique almost eliminated anesthetic deaths. All surgery was performed by one of us (TEM, Jr.). During a fellowship year in London prior to this project, the surgeon had performed more than 150 rabbit penetrating keratoplasties. Thus the surgical technique was standardized and a high degree of reproducibility had been achieved. All keratoplasties were performed under the Zeiss diploscope.

The procedure consisted of the placement

TABLE 40

COMPOSITION OF EXPERIMENTAL GROUPS

| Group | Suture | Total Eyes | Donor Allograft | Total Eyes | Donor Autograft |
|---|---|---|---|---|---|
| IA. Albino | 8-0 silk | 16 | Albino | 12 | Same |
| IB. Albino | 10-0 Ethilon | 15 | Albino | 15 | Same |
| IIA. Albino | 8-0 silk | 15 | Pigmented | 14 | Same |
| IIB. Albino | 10-0 Ethilon | 18 | Pigmented | — | |
| IIIA. Pigmented | 10-0 Ethilon | 14 | Pigmented | 14 | Same |
| IVA. Pigmented | 8-0 silk | 13 | Albino | 12 | Same |
| IVB. Pigmented | 10-0 Ethilon | 14 | Albino | 13 | Same |

of a 5.0 mm penetrating corneal button with 12 direct appositional interrupted sutures. After the animal was anesthetized, the eyelids and the eye were retracted with stay sutures. A 5.0 mm trephine button was outlined in the center of the host rabbit cornea. A donor button was then cut from the eye of a rabbit killed immediately before surgery. A 5.0 mm donor button was prepared with trephine and scissors. The recipeint button was prepared in similar fasion. Following this, the donor button was positioned in the recipient eye and stay sutures were placed (8-0 virgin silk or 10-0 Ethilon) in the three, six, nine, and 12 o'clock meridians. Two additional interrupted sutures were then placed in each quadrant. If fibrin-clotted aqueous presented in the wound, it was removed with forceps or a sponge (heparin was not used to prevent clotting). The chamber was allowed to reform spontaneously. If a chamber did not reform, sutures in the area of the leak were replaced. Following the allograft, most animals received a rotational autograft in the opposite eye, with the same procedure used throughout, except that the donor button, after being cut, was rotated through 180°. At the end of the second procedure, the animal was cycled on oxygen until he was conscious. One drop of phenylephrine HCl 10%, polymyxin B, and cylclopentolate was placed in each eye and the animal was returned to its cage.

*Postoperative treatment and evaluation*—After surgery, animals received topical polymyxin B to each eye twice daily for two days, after which no further medication was given. They were observed twice weekly until the sutures were removed (at approximately 14 days); they were seen daily for three days after removal of the sutures and thereafter at weekly intervals. All examinations were made by slit lamp microscopy. Slit lamp evaluation is imperative during the first 17 postoperative days because the cause of graft failure usually can be diagnosed during this period.

*The early graft reaction*—In the rabbit, the early graft reaction may begin as soon as the second postoperative day and may continue until the 60th day. Because of this range, and because sutures must be removed sooner in the rabbit (about 14 days) than in man, the early graft period has been delineated arbitrarily as lasting until the 75th day. The maximal reaction seems to occur between the seventh and 21st day, much earlier than in man. Degree of reaction among animals varied markedly (Fig. 19). The clinical course of these reactions has been defined as mild, moderate, severe, and permanent donor opacity. In mild reactions, the inflammatory response was limited to the donor-host junction. When neovascularization occurred, it rarely extended beyond the recipient margin. The central cornea remained free of inflammation (Fig. 19-A and 20-A). In moderate reactions, inflammatory edema extended throughout the recipient and donor cornea; neovascularization extended into the peripheral donor cornea, but not into the central donor. With quiescence, most of the donor cornea is clear (Fig. 19-B and 20-C).

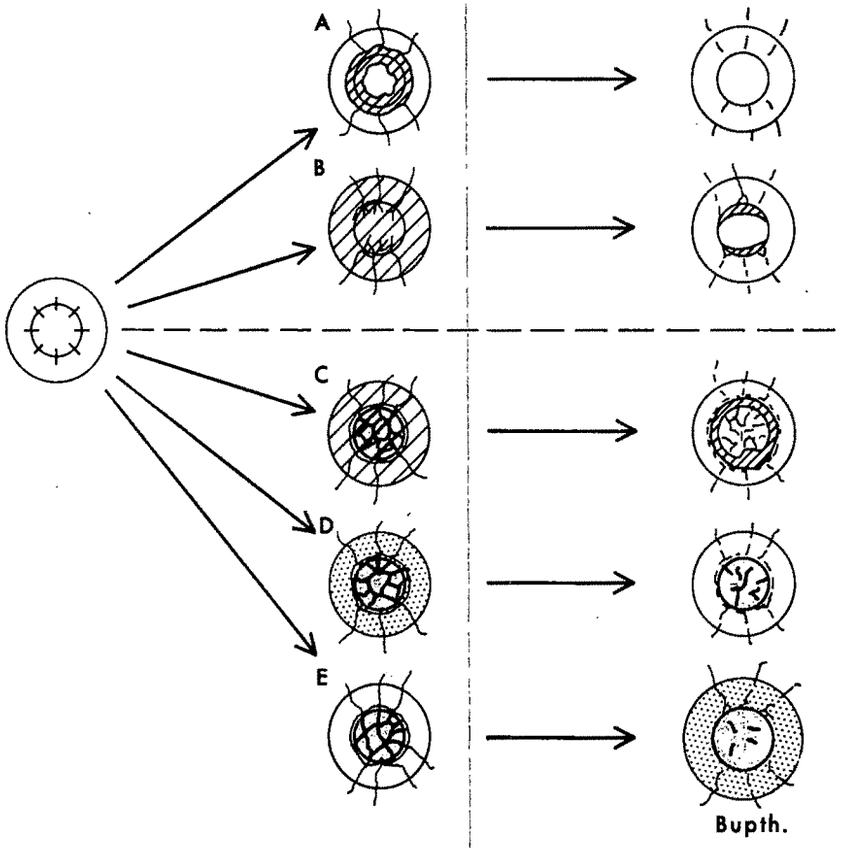



Fig. 19 (Moore and Aronson). Clinical patterns of graft reaction in the rabbit. (A) Mild reaction with minimal structural change. (B) Moderate reaction in which some degree of structural change occurs in the peripheral donor cornea. (C) Severe reaction in which the donor cornea clears following resolution of active inflammation. (D) Severe reaction in which residual scarring and atrophy of the donor cornea are present. (E) Severe reaction in which buphthalmos has occurred.

In severe reactions, both inflammatory opacity and neovascularization pervade the recipient and donor corneas. If the central area of the donor cornea clears when inflammation subsides, it often gives the impression of being transparent (Fig. 19-C and 20-E); however, slit lamp examination will reveal scarring and ghost vessel formation. If the donor cornea does not clear when inflammation subsides, it has incurred permanent opacification. As a rule, the donor cornea is a shrunken, atrophic graft (Fig. 19-D) or it is thinned in a buphthalmic eye (Fig. 19-E and 20-G). Histologic evaluation of mild reactions revealed scarring at the donor-host junction (Fig. 20-B). Neovascularization extending through the host cornea and involving the donor-host junction was observed in moderate reactions (Fig. 20-D). In severe reactions, distinct evidence of neovascularization and scarring in the donor graft was seen (Fig. 20-E). In atrophic grafts, a small, heavily scarred button was present. In buphthalmos, the principal characteristic was marked scarring accompanied by severe active inflammation (Fig. 20-H).

We have defined a successful graft in the rabbit according to that classification in man —i.e., one that is entirely clear with the exception of the suture tracts. The mild and moderate graft reactions yield successful grafts. The severe and opaque graft reactions are classified as failures, although the

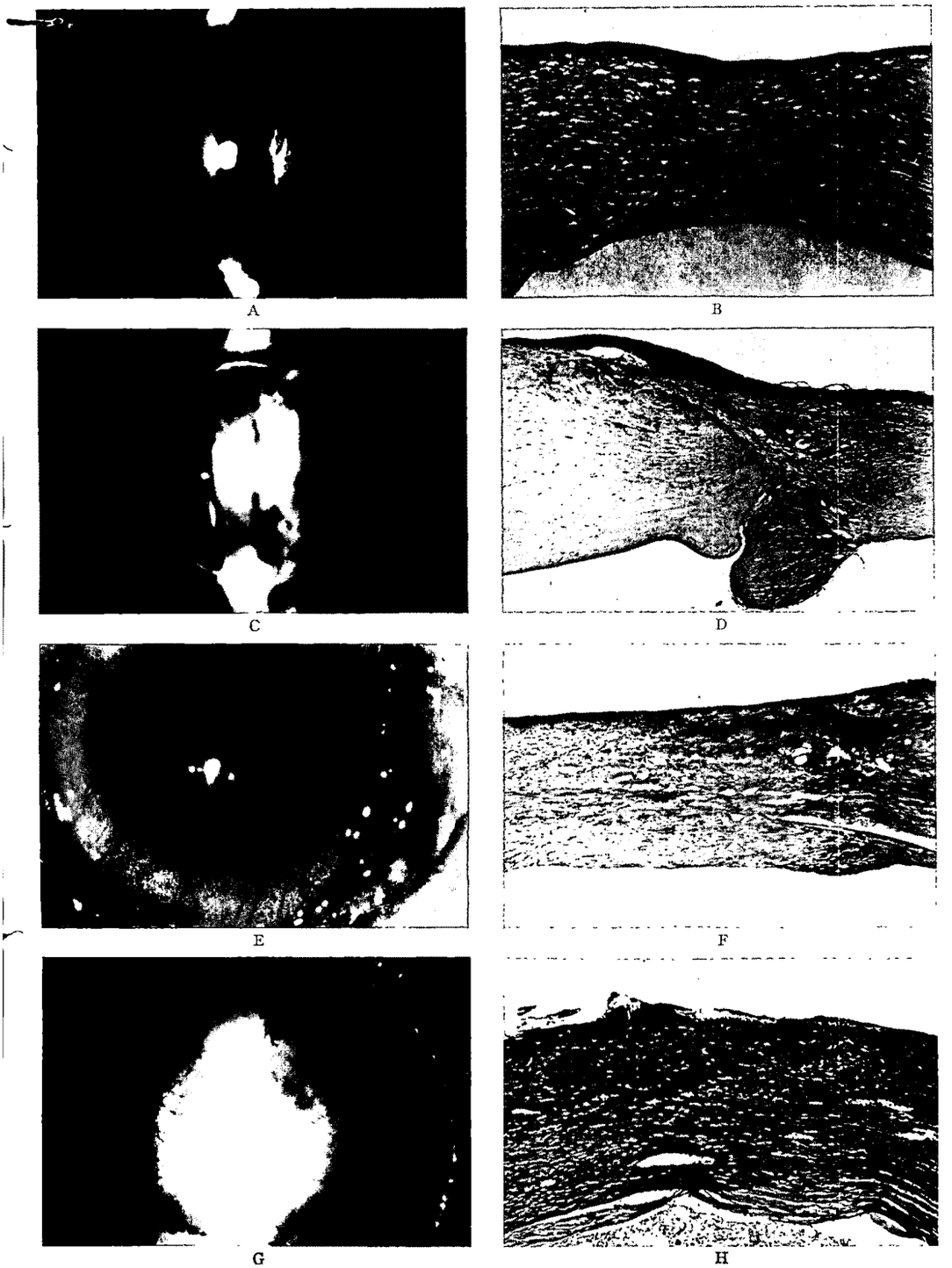



Fig. 20 (Moore and Aronson). Patterns of early graft reactions in the rabbit. (A) Mild reaction, 75 days postsurgery. (B) Histology of mild corneal reaction (×25). (C) Moderate reaction, 83 days postsurgery. (D) Histology of the same cornea (×25). Note neovascularization and fibrous proliferation in the host cornea. (E) Severe reaction 90 days postsurgery. Note clear cornea superiorly. (F) Histology of the same cornea (×25). Note neovascularization and lymphoid proliferation in the host cornea. (G) Buphthalmos, 78 days postsurgery. (H) Histology of the same eye (×25). Note severe inflammatory response throughout the donor cornea.

severe reaction eventually clears and presents an apparently clear donor graft. This eventual clearing results from the unique regenerative property of the rabbit endothelium.[1,2] While rabbit donor endothelium is destroyed in the course of a severe graft reaction, unlike human endothelium,[3] it regenerates from the host cornea following inflammatory resolution with clearing of the donor graft. For purposes of analogy, in the rabbit experiments, a severe reaction has been classified as an early graft failure.

### Causes of graft failure

Earlier in this report, we identified five potential causes of early graft failure in man. The first four, namely, primary donor failure, surgical trauma, suture toxicity, and microbial toxicity, were identified by a specific clinical and morphologic picture or a culture. The last, tissue incompatibility, was identified only after the other causes of graft failure could be excluded. A simultaneous autograft in each animal provided a concurrent histocompatibility control for evaluating this reaction. Only animals demonstrating a clear autograft and failed allograft were considered to manifest tissue incompatibility reactions.

*Surgical failure*—This presented a typical clinical picture. During the first several days after surgery, some derangement of the anterior chamber was evident. This included an absent chamber, fibrin hypopyon or hyphema in the chamber, and intrusion of the lens or iris into the wound. By the seventh to 10th day, intraocular pressure increase could be identified by haziness of the donor cornea on slit lamp examination, tautness of sutures with evidence of cutting into donor and recipient tissue, and firmness of the eye on tactile evaluation. Wound dehiscences began to appear by the 14th day (Fig. 21-A). If, according to protocol, sutures were removed at this time, the incidence of wound dehiscence markedly increased and prolapse of intraocular contents occurred (Fig. 21-B). If sutures were not removed, buphthalmos appeared about the 21st day, and occurred in almost every failure by the 50th day.

*Suture toxicity*—Toxicity to 8-0 silk suture was discernible as early as the fourth postoperative day. It presented initially as a dense white infiltrate throughout the suture tract. This rapidly progressed (at seven to 10 days) to neovascularization of the suture tract (Fig. 21-C), frequently extending into the central cornea and leading to graft failure (Fig. 21-D). When 10-0 Ethilon suture was used, the degree of infiltrate formation was markedly reduced (Fig. 21-E); however, superimposition of indigenous bacterial flora along the suture tract occasionally led to neovascularization of the tract but rarely caused graft failures.

*Bacterial infection*—This category is divided into pathogenic and indigenous subgroups. Conjunctivae were cultured routinely before surgery and at the time of sacrifice. Animals demonstrating a suspected bacterial lesion were cultured at the time of such identification. All cultures were plated on blood and chocolate agar and read at 24 hours.

A pathogenic microbial infection presented clinically as a suture tract abscess (Fig. 21-G). If the abscessed suture was removed early in the course of inflammation, graft failure usually could be prevented. Pathogenic microbes identified as causative inflammatory agents in this study include Staph. aureus, beta hemolytic streptococcus, and Pseudomonas aerugenosa.

Reactions caused by indigenous bacterial toxicity could be diagnosed only in nylon-sutured rabbits since the reaction is identical to that caused by silk suture toxicity. This reaction appears about the eighth postoperative day and is indicated initially by infiltrates surrounding the suture tracts. Suture tracts rapidly vascularize. In our series, such a reaction did not progress to total corneal neovascularization, probably because sutures were removed by the 14th day. Epithelial closing of the suture tract prevents bacterial entry, thereby halting progression of the inflammation. The predominant microbes re-

sponsible for this reaction were Hauch mimae and Moraxella nonliquefaciens.

*Tissue incompatibility*—Our previous discussion has indicated that tissue incompatibility could be diagnosed only after the other variables were controlled; thus, it could be identified only in nylon-sutured animals without evidence of surgical failure or microbial toxicity. The reactivity of indigenous bacteria delays precise identification of the reaction until the sutures are removed. We have limited the identification to animals with a simultaneous autograft which remained nonreactive. The earliest detectable onset of this reaction is between two and one-half and three weeks after surgery. The reaction is characterized by infiltrate formation, first in the periphery, then extending throughout the corneal stroma. The reaction appears to originate in the limbus, since the anterior chamber is relatively quiet. As the reaction progresses, extensive neovascularization extends first into the peripheral donor cornea and then throughout the corneal stroma. These reactions usually progress to a severely shrunken, scarred cornea or to buphthalmos (Fig. 21-H). Occasionally, a cornea will demonstrate involuted blood vessels and clearing of the corneal stroma until a clear donor graft is achieved.

Corneal histopathology has been exceptionally well characterized for the graft reaction in the rabbit.[4-6] In no circumstance, however, can types of graft failure be differentiated by histopathologic configuration. Although histologic changes were studied in numerous eyes in this series, they did not prove as useful as sequential clinical and morphologic evaluations.

*Delayed graft reaction*—In the rabbit, this refers to inflammatory reactions of the donor cornea which occur any time after 75 days (the end of the early graft period). A delayed graft reaction is one that occurs in a previously quiet eye. Onset of the active stage features injection of the recipient vessels and extension of inflammatory edema into the donor cornea. With progression to the severe stage, neovascularization of the donor cornea occurs. In delayed graft failure, this stage invariably proceeds to buphthalmos. In a certain number of animals, the graft cleared spontaneously after the delayed graft reaction became inactive.

TABLE 41

GRAFTED EYES EVALUATED FOR SPONTANEOUS DELAYED GRAFT REACTIONS

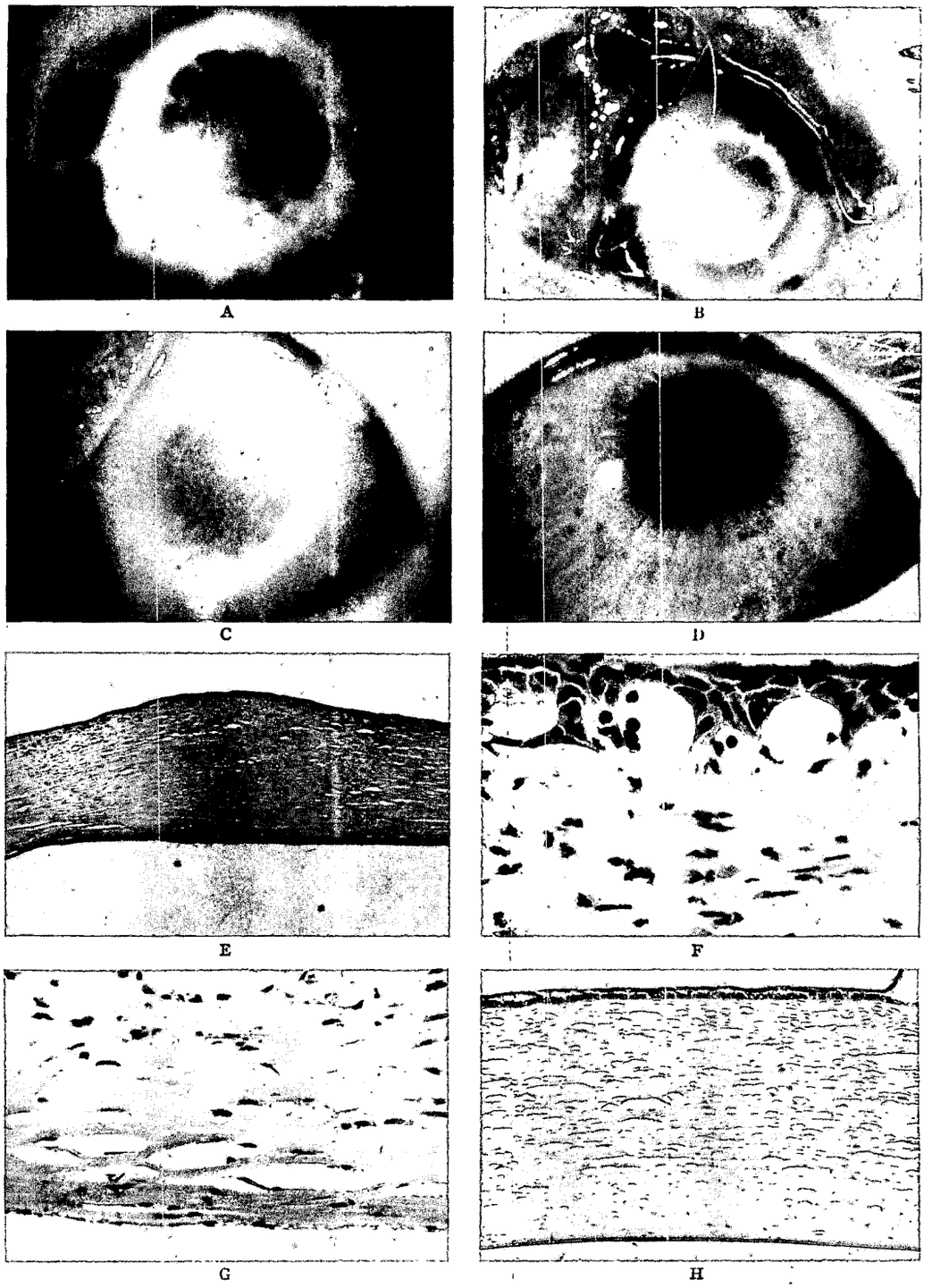
| Follow-up Time | Allograft Eyes | Autograft Eyes | Total Eyes |
|---|---|---|---|
| One month or less | 5 | 3 | 8 |
| One to two months | 8 | 9 | 17 |
| Two to three months | 15 | 10 | 25 |
| Three to four months | 6 | 0 | 6 |
| Four to five months | 12 | 12 | 24 |
| Five to six months | 4 | 2 | 6 |
| Six months or more | 8 | 5 | 13 |
| Total eyes | 58 | 41 | 99* |

* This number of grafts was performed in 73 animals.

Two types of study of the delayed graft reaction were undertaken. The first study evaluated the total number of delayed graft reactions which occurred spontaneously in animals with successful grafts in the early period. In the second study, animals whose grafts were successful throughout the early period were immunized systemically and then challenged by conjunctival instillation of the immunizing antigen.

*Spontaneous inflammation*—In the first study, which dealt with spontaneous inflammation, 73 animals (99 eyes) were followed for seven months after the end of the early graft period (Table 41). During this period, gross cage inspection was made weekly and slit lamp examinations were made biweekly. When a delayed graft reaction was detected, the animal was monitored by slit lamp examination every other day throughout the course of active inflammation. If the reaction had not cleared by the end of the eighth week, the animal was classified as a delayed graft failure (Fig. 22-A and B).

Animals with delayed reactions were cul-


A
B
C
D
E
F
G
H

tured for bacteria when the reaction was first identified. Swab cultures were taken from the inferior conjunctival fornix of both eyes and plated on blood and chocolate agars. Cultures were read and identified at 24 hours.

Histologic changes in the delayed graft reaction were difficult to differentiate from those in the immediate reaction. The acute phase of inflammation demonstrated a diffuse polymorphonuclear (PMN) leukocyte reaction throughout the corneal stroma. Other findings included marked engorgement of blood vessels and a moderate anterior chamber inflammatory response. As inflammation subsided and buphthalmos developed, thinning and scarring of the donor cornea with epithelial edema became apparent.

Some variables which may be operative in predisposing to delayed graft reactions were evaluated in the spontaneous reaction group. The stimulus was evaluated by conjunctival culture. Host response was evaluated by comparing the number of pigmented and albino animals which manifested reactions. The effect of structural change in predisposing to subsequent inflammation was evaluated by classifying the degree of neovascularization in the recipient cornea. The classifications were: (1) absent, (2) mild (in which a single vascular branch extended into the host cornea), and (3) moderate (in which a network of vessels extended into the host cornea and encircled the donor graft). This classification closely paralleled that already described for the postoperative graft in the patient series.

The effect of particular variables in the early graft reaction was also evaluated in the spontaneous reaction group. These variables included suture toxicity and tissue incompatibility. The former was a comparison of silk and nylon sutures, the latter a comparison of allo- and autografts.

*Exogenous stimulation*—These experiments were performed in 30 rabbits which had survived the period of observation for spontaneous inflammation without evidence of a delayed graft reaction. Animals were selected on the basis of degree of structural change and neovascularization in the host cornea. They were divided into groups according to whether these reactions were: (1) absent, (2) minimal, or (3) moderate. A similar number of allo- and autograft corneas were divided into the three structural groups (Table 42).

Animals were systemically immunized to bovine serum albumin (BSA) by weekly injections of 0.1 ml (10 mg BSA in Freund's adjuvant, equal parts) into four intradermal sites. Following the fourth injection, all animals were titered for anti-BSA by reverse radial diffusion.[7] They were subsequently challenged by the topical instillation of BSA (100 mg/ml, 4 drops, 5 mg per drop) into each conjunctival sac every two hours at eight-hour intervals for 10-day periods. Animals were examined daily throughout this challenge period by slit lamp microscopy. The earliest discernible change was limbal injection and infiltrative clouding of the host cornea. This progressed to involve the donor cornea first by focal infiltrates, and later by

Fig. 22 (Moore and Aronson). The delayed graft reaction in the rabbit. (A) A spontaneous delayed graft reaction in an albino allograft six and one-half months after surgery. (B) A spontaneous delayed graft reaction in an albino autograft five months after surgery. (C) A delayed graft reaction following topical challenge with BGG. (D) The nongrafted eye of the same animal, showing absence of corneal inflammation following topical BGG challenge. (E) Histology of cornea in Figure C, showing the diffuse inflammatory response throughout the donor cornea (×16). (F) Same cornea (×150), PMN proliferation throughout the anterior stroma and epithelium. (G) Same cornea (×150), PMN proliferation throughout the posterior stroma and endothelium. (H) Histology of cornea in Figure D. Note absence of inflammatory response.

TABLE 42

SELECTION OF ANIMALS FOR EXOGENOUS IMMUNOGENIC STIMULATION

| Structural Group | Allograft | Autograft | Total Eyes |
|---|---|---|---|
| No host neovascularization | 10 | 9 | 19 |
| Mild neovascularization | 8 | 7 | 15 |
| Moderate neovascularization | 7 | 19 | 26 |
| Total eyes | 25 | 35 | 60 |

diffuse stromal clouding. Most animals were killed and their eyes enucleated by the end of the 10-day period. However, two animals (one allograft, one autograft) that demonstrated relatively severe stromal inflammation were continued on topical medication as described above for 15 additional days. Both animals developed buphthalmos.

Histologic observations on the corneas of these animals were much the same as in the spontaneous delayed graft reaction group. In the early stages, a marked lymphoid hyperplasia was noted around the limbal vasculature. PMN proliferation occurred throughout the host cornea, entering minimally into the donor cornea. In more severe reactions, PMN's were diffused throughout the corneal stroma; distinct endothelial involvement was also present. The animals which had been allowed to develop buphthalmos demonstrated the severe changes described above as characteristic of buphthalmic eyes.

A second experiment was designed to demonstrate differences between the reactions of grafted and nongrafted eyes to topical immunogenic stimulation. Fourteen animals with monocular grafts were divided into two groups: nine with no changes and five with mild changes. They were immunized systemically to bovine gamma globulin (BGG) in Fruend's adjuvant, in a dosage and schedule similar to the previous experiment. BGG was selected because it does not produce corneal stromal disease in a nontraumatized eye.[8] Following immunization, all animals were challenged bilaterally with topical BGG (100 mg/ml) and followed by slit lamp as described previously for the BSA model.

Changes in the grafted eye were similar to those described in the BSA experiment. Corneal infiltrates and severe corneal clouding occurred (Fig. 22-C). The nongrafted eye demonstrated only limbal hyperemia; there was no evidence of corneal inflammatory disease (Fig. 22-D).

At the end of the 10th day, animals were killed, the eyes enucleated and prepared for histology. Histologic evaluation revealed corneal changes which conformed to the described clinical picture. The focal infiltrates appeared as discrete clumps of PMNs. A diffuse PMN reaction was noted in severe stromal disease (Fig. 22-E). PMNs extended into donor epithelium (Fig. 22-F) and endothelium (Fig. 22-G), leading ultimately to delayed graft failure. The nongrafted cornea was free of a PMN response (Fig. 22-H).

These experiments were undertaken to demonstrate that an exogenous immunogenic challenge can produce a delayed graft reaction. This reaction has been compared to (1) the degree of immune response and (2) the amount of structural change exhibited by the challenged animals.

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Overall results during the early graft period have been expressed in Table 43. The difference between autograft and allograft success is 9%. When only simultaneous auto-allograft animals are counted, the difference is 12%. In a single-variable experiment, this difference (9 to 12%) would account for tissue incompatibility failures; however, the remaining 45% of graft failures must be accounted for. Analysis of an individual variable required that each variable be controlled independently.

*Silk suture toxicity*—This appeared to account for a majority of all graft failures. When silk and nylon suture groups (all autografts) are compared, success rates for the two sutures are 32 vs 76%, respectively. (Table 44). If the silk–nylon comparison is limited to all allografts, the difference is pronounced: 18 vs 69%. However, if the most reactive group (group IV, albino donor, pigmented recipient) is evaluated, the divergence is dramatic: 92% clear nylon vs 23% silk for autografts, and 43% nylon vs 0% silk for allografts. Since the choice of suture material so strongly affected the degree of graft success, it was obvious that subsequent variables could be evaluated only in nylon-sutured grafts.

*Surgical trauma*—Evaluation of surgical trauma as the cause of graft failure indicates that 55% of allograft failures and 100% of autograft failures can be attributed to a surgical cause (Table 45). This category includes cases with a persistently flat chamber, early wound dehiscence, or early-onset buphthalmos. In general, evidence for surgical failure was identifiable between the second and seventh postoperative day.

*Pathogenic bacteria*—Staph. aureus and beta hemolytic streptococcus produced suture tract abscesses which resulted in one opaque graft and one severe graft reaction and accounted for 10% of failed grafts.

*Nonpathogenic bacteria*—These were not identified as the primary cause of any graft failure in this series. However, a number of nylon-sutured cases demonstrated neovascularization of the suture tracts. When sutures were removed, the inflammatory reaction ceased and vessels involuted. Prolific growths of indigenous bacteria (H. mimae, moraxella) were cultured from the conjunctival sac of each of these animals.

*Tissue incompatibility*—As it was in the patient series, tissue incompatibility was diagnosed by exclusion. In this series, following elimination of silk-sutured cases, 35% of all graft failures were most likely due to tissue incompatibility factors. However, when evaluating the most reactive experimental group (group IV), the percentage of failures is increased to 75%. A tissue incompatibility graft failure also occurred in group II. Within-strain grafting (groups I and III) demonstrated no evidence of tissue incompatibility.

Table 46 presents an approximation of the incidence of graft failure attributable to each variable in this penetrating keratoplasty se-

TABLE 43

RESULTS IN RABBIT KERATOPLASTY (UNCORRECTED)

| Graft Classification | Total Eyes | Success | | Failure | | % Clear |
|---|---|---|---|---|---|---|
| | | Mild | Moderate | Severe | Opaque | |
| Total allografts | 105 | 31 | 17 | 16 | 41 | 46 |
| Controlled allografts | 80 | 20 | 14 | 13 | 33 | 43 |
| Autografts | 80 | 29 | 15 | 13 | 23 | 55 |

TABLE 44

ROLE OF SUTURE IN GRAFT FAILURE

| Graft Classification | | Total Animals | Success | | Failure | | % Clear |
|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | Opaque | |
| I. Albino donor, albino recipient | | | | | | | |
| Silk suture | Allograft | 16 | | 2 | 9 | 5 | 13 |
| | Autograft | 12 | 1 | 2 | 6 | 3 | 25 |
| Ethilon suture | Allograft | 15 | 9 | 1 | 2 | 3 | 67 |
| | Autograft | 15 | 8 | 1 | 1 | 5 | 60 |
| II. Pigmented donor, Albino recipient | | | | | | | |
| Silk suture | Allograft | 15 | 2 | 4 | 3 | 6 | 40 |
| | Autograft | 14 | 3 | 2 | 4 | 5 | 36 |
| Ethilon suture | Allograft | 18 | 11 | 2 | 1 | 3 | 72 |
| III. Pigmented donor, pigmented recipient | | | | | | | |
| Ethilon suture | Allograft | 14 | 8 | 3 | 1 | 2 | 78 |
| | Autograft | 14 | 6 | 5 | 1 | 3 | 78 |
| IV. Albino donor, pigmented recipient | | | | | | | |
| Silk suture | Allograft | 13 | | | 1 | 12 | 0 |
| | Autograft | 12 | 1 | 3 | 2 | 6 | 33 |

TABLE 45

ROLE OF SURGERY, PATHOGENIC BACTERIA, AND TISSUE INCOMPATIBILITY IN GRAFT FAILURE

| Graft Classification | Total Failures | | Surgical Failure | | | Bacterial Failure | | | Tissue Incompatibility | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Severe | Opaque | Severe | Opaque | % | Severe | Opaque | % | Severe | Opaque | % |
| I. Allograft | 2 | 3 | 1 | 3 | | 1 | 0 | | 0 | 0 | |
| Autograft | 1 | 5 | 1 | 5 | | 0 | 0 | | — | — | |
| II. Allograft | 1 | 3 | 1 | 2 | | 0 | 0 | | 0 | 1 | |
| III. Allograft | 1 | 2 | 1 | 1 | | 0 | 1 | | 0 | 0 | |
| Autograft | 1 | 3 | 1 | 3 | | 0 | 0 | | — | — | |
| IV. Allograft | 0 | 8 | 0 | 2 | | 0 | 0 | | 0 | 6 | |
| Autograft | 0 | 1 | 0 | 1 | | 0 | 0 | | — | — | |
| Total Allograft | 4 | 16 | 3 | 8 | 55 | 1 | 1 | 10 | 0 | 7 | 35 |
| Total Autograft | 2 | 9 | 2 | 9 | 100 | 0 | 0 | 0 | — | — | — |

| Graft Classification | | Total Animals | Success | | Failure | | % Clear |
|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | Opaque | |
| IV. (Cont'd) | | | | | | | |
| Ethilon suture | Allograft | 14 | 1 | 5 | | 8 | 43 |
| | Autograft | 13 | 10 | 2 | | 1 | 92 |
| Totals | | | | | | | |
| Silk suture | Allograft | 44 | 2 | 6 | 13 | 23 | 18 |
| | Autograft | 38 | 5 | 7 | 12 | 14 | 32 |
| Ethilon suture | Allograft | 61 | 29 | 12 | 4 | 16 | 69 |
| | Autograft | 42 | 24 | 8 | 2 | 9 | 76 |

TABLE 46

INCIDENCE OF FAILURE DUE TO SEVERAL VARIABLES IN PENETRATING ALLOGRAFTS

| Variable | Total Eyes | % Opaque Corneas with Severe Reaction |
|---|---|---|
| Suture reaction | 105 | 61 |
| Surgical trauma | 61* | 22 |
| Pathogenic bacteria | 61* | 4 |
| Tissue incompatibility | 61* | 13 |

* Evaluation limited to Ethilon suture series.

ries. As mentioned, silk suture was the prevalent cause of failure, producing 61% failure in the allograft series. (These data were obtained by calculating the difference between success rates in the silk and nylon suture series. This assumes that the only difference in these two series was the suture material. Other suture-related variables may play a role in this extraordinary difference.)

Surgery, pathogenic bacteria, and tissue incompatibility were evaluated only in the nylon suture series. Surgical failure occurred in 22% of allografts. Pathogenic bacteria were responsible for graft failure in 4% of cases. And tissue incompatibility occurred in approximately 13% of allografts. As noted, we did not feel that the role of nonpathogenic bacteria could be evaluated accurately in this study. In descending order the ratio of failure is suture toxicity—61%, surgical trauma—22%, tissue incompatibility —13%, and bacterial infection—4%.

## RESULTS

The use of the rabbit as an experimental model for penetrating keratoplasty is not entirely satisfactory. Several factors complicate surgical technique in the rabbit: corneal thinness, a relatively shallow anterior chamber, and rapid fibrin clotting in the aqueous during surgery. Inflammatory reactivity is considerably greater in the postoperative period; wound healing is markedly faster. The normal rabbit eye is often bacteriologically sterile but once inflammation occurs, bacterial contamination by indigenous microbes develops. The incidence of pathogenic bacteria is much greater in the rabbit series than in the human. Finally, unlike the human cornea, the endothelium of the rabbit host cornea regenerates following inflammation, a characteristic which can render an opaque graft apparently clear.

These properties limit the applicability of findings in rabbit experiments to problems in the human graft. First, distinctly defined criteria for the course of postoperative inflammation are essential to determining the success or failure rate of keratoplasties. The mild or moderate clinical course produces a successful graft. The mild reaction is characterized by inflammation adjacent to the wound margin only; it is analogous to mild or moderate graft reactions in man. The moderate reaction shows haze throughout the donor cornea. Centrally, the reaction is in the anterior corneal stroma. Peripheral neovascularization extends to the central margin of donor sutures, but never into the central donor cornea. This reaction is analogous to a severe inflammatory reaction in man. As noted earlier, a successful human graft can be achieved if the endothelium is protected from severe central inflammation. For purposes of this study, a mild or moderate reaction is classified as a successful graft.

Aspects of graft failure in the rabbit do not satisfactorily compare to the clinical graft experience. Obviously, the opaque donor corneas and buphthalmos are acceptable as failures. However, a severe reaction in a clear donor graft is designated as a graft failure in man. The course of this reaction features a severe inflammatory response throughout the entire donor cornea; neovascularization extends throughout the central cornea; endothelial involvement by the inflammatory process is uniform. At this stage the donor cornea is completely opaque. Such a reaction invariably goes on to donor failure in man. In the rabbit, however, such a reaction can go on to graft failure or it can eventually clear with the disappearance of active inflammatory signs. Central blood vessels involute and become ghost vessels. The donor endothelium can regenerate with host cells and a viable graft can result. Because this kind of reaction does not occur in man, we have considered this group of cases to represent graft failure.

*Variables*—Suture toxicity was considered a supravariable in this series, since the experiments could not be completed until silk suture toxicity had been controlled and overcome. As noted in Table 44, this proved to be especially true in group IV animals (albino donor, pigmented recipient) where all allografts sutured with silk resulted in failure. Obviously, other variables could not be evaluated in such a circumstance. The distinct features of suture toxicity have been evaluated at length in previous studies.[1-3] With adoption of nylon suture, suture toxicity was eliminated as a significant variable in this series.

Of the other variables evaluated in nylon-sutured animals, the surgical procedure appeared to be the most important in graft success. To evaluate the significance of the surgical procedure, we attempted to simulate the clinical procedure as closely as possible. To avoid introducing another variable to our multiple variable analysis, we did not use anticoagulants or other agents that could have altered the reproducibility of the original procedure. This may explain the relatively high incidence of surgical failure in contrast to other reported series.[4,5]

A surgical failure could be identified with considerable precision. The signs of surgically induced inflammation appeared very early as anterior chamber fibrin, hemorrhage, inflammation, or wound problems. Sequelae to these early signs followed rapidly, almost always manifested by an increase in intraocular pressure (donor haze or wound rupture). As noted, these invariably led to buphthalmos. We believe that this pattern of events could not be related to any of the other variables, principally because of the rapid onset following keratoplasty.

The role of infection by pathogenic bacteria was clearly distinguishable. The corneal lesion appears as a suture tract infection which spreads to envelop the entire cornea. The lesion in the rabbit is identical to the lesion in the human.[6] Its incidence was minimal, 4% in this series. The source of infection was identified by culture.

Indigenous bacteria were implicated earlier as a more significant factor in enhancing corneal graft reactions. In interrupted nylon suture grafts, this lesion appeared as infiltrate and as neovascularization of suture tracts and necessitated early removal of sutures. H. mimae was the prevalent agent involved; prolific numbers of organisms were noted in animals with the above described reactions. A distinct graft failure which is directly attributable to such organisms is extremely difficult to demonstrate, insofar as similar changes occur in the early tissue incompatibility reaction. Rather, we have considered indigenous bacteria to be a secondary modifier, which tends to heighten or precipitate the overall graft reaction, but probably in itself does not produce graft failure.

Tissue incompatibility as a factor in graft failure was evaluated by two methods. The first was an overall series comparison between allo- and autografts in the same animals, yielding a 12% difference in allograft failure (Table 42). The second was identification of tissue incompatibility reactions in the nylon-sutured allograft series. In this case, 13% of grafts failed because of this factor (Table 45). (It should be reiterated that the tissue incompatibility reaction was principally a diagnosis of exclusion, and identification was made only after the other known variables were ruled out.) The close approximation of 12 to 13% tissue incompatibility reaction, derived from two different techniques of evaluation, strongly supports this figure as the incidence of tissue incompatibility in these rabbit penetrating keratoplasty experiments.

Of particular interest is the identification of the onset of a tissue incompatibility reaction. By selecting distinctly different strains of rabbits, we were able to heighten the level of graft failure due to tissue incompatibility. In allografts done within a strain (i.e., group I, albino donor–albino recipient, and group III, pigmented donor–pigmented recipient) no tissue incompatibility reactions were identifiable. However, they were identified in cross-strain allografts. In group IV, albino donor–pigmented recipient, 43% of grafts failed because of this factor, while in group II, pigmented donor–albino recipient, 11% failed because of it. It seems probable that genetic factors play a major role in producing ocular tissue incompatibility reactions as in kidney and heart transplants.[7-9] The cross-strain grafts reacted more severely than the in-strain grafts, the former resembling cross-grafting reactions in heterologous species[10,11] and the latter much like isologous strains.[12,13]

As already noted, these rabbit strains were selected because of their extensive inbreeding over a period of years. In previous experiments,[14,15] we reported the increased immunogenic inflammatory reactivity demonstrated by the pigmented rabbit in contrast to the albino when challenged with pure protein antigens. In these experiments, the pigmented animal demonstrated extreme reactivity to silk suture. It seems likely that the higher incidence of tissue incompatibility reactions in pigmented animals accounts for the increased inflammatory reactivity which seems characteristic of this strain. This does

not rule out the remote possibility that the reaction in pigmented animals is due to increased antigenicity of the albino donor cornea.

Primary donor failure, described as a cause of human graft failure, does not pertain to these experiments since donor tissue was taken from relatively young animals and used immediately after death.

The disparity between our keratoplasty failure rates in the rabbit and those of other authors[4-6] probably results from the experimental goals of the different groups. Our objective was to evaluate the role of all variables in graft failure. Other groups focused on the tissue incompatibility reaction, setting up techniques purposely to exclude other variables. Also, to the best of our knowledge all other groups did in-strain grafting (many employing lamellar keratoplasties), most frequently albino-to-albino. Perhaps our results would comply with those of other reports had we not attempted to exclude these biases from our series.

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A majority of spontaneous delayed graft reactions (16 of 20) occurred in the initial two-month period (Table 47). Only four reactions occurred after the second month. (However, most animals were observed in the initial early graft period.) When corrected for percentage of occurrence (percent failure in all animals), the incidence of spontaneous delayed reactions gradually diminishes with time. A rate of 13% for the first month after the early graft period had ended decreased to an average of 2% for the following two-month intervals.

The principal variable relating to occurrence of the delayed graft reaction was bacterial infection (Tables 48 and 49). Sixty percent of reactions (66% of failures) demonstrated a pathogenic bacterium on culture. The predominant aggravating microbe was Staph. aureus. Florid cultures of nonpathogenic bacteria were recovered from all but one of the remaining eyes. In this case, moraxella was the predominant organism. (We describe moraxella as a nonpathogen in the rabbit because active inflammation is seldom seen in the rabbit cornea although cultures are positive.)

The role of suture toxicity in predisposing to the delayed graft reaction was again evaluated (Table 50). A preponderance of delayed graft reactions occurred in animals with silk-sutured (8-0 virgin silk) grafts. Only 9% of nylon-sutured grafts demonstrated a delayed reaction and none of these went on to failure.

The effect of silk suture in predisposing to delayed failure is probably related to the degree of altered host structure still present at

TABLE 47

OCCURRENCE OF DELAYED GRAFT REACTIONS, BY MONTH

| Follow-up Time | Eyes Followed | Allograft | Autograft | Total Reactions | |
|---|---|---|---|---|---|
| | | | | No. | % |
| One month or less | 99 | 5 | 8 | 13 | 13 |
| Two to three months | 74 | 1 | | 1 | 1 |
| Three to four months | 49 | 1 | | 1 | 2 |
| Four to five months | 43 | | 1 | 1 | 2 |
| Five to six months | 19 | | 1 | 1 | 5 |
| Six months or more | 13 | | | 0 | 0 |
| Total | 99 | 8 | 12 | 20 | 20 |

TABLE 48

ISOLATION OF PATHOGENIC BACTERIA FROM THE CONJUNCTIVA IN DELAYED GRAFT REACTION

| Classification | Total Reactions | Pathogenic Bacteria* | |
|---|---|---|---|
| | | No. | % |
| Delayed reaction | 20 | 12* | 60 |
| Delayed failure | 9 | 6 | 66 |

* Staph. aureus was isolated from 11 eyes, beta hemolytic streptococcus from one eye.

TABLE 49

ISOLATION OF NONPATHOGENIC BACTERIA FROM DELAYED GRAFT EYES FREE OF PATHOGENIC BACTERIA

| Classification | Total Reactions | Nonpathogenic Bacteria* | |
|---|---|---|---|
| | | No. | % |
| Delayed reaction | 8 | 7* | 87 |
| Delayed failure | 3 | 3 | 100 |

* Moraxella liquefaciens was isolated from five eyes, H. mimae from two.

TABLE 50

OCCURRENCE OF DELAYED GRAFT REACTIONS, SILK VS NYLON SUTURE

| Suture Group | Total Animals | Reaction | | Failure | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Silk | 52 | 16 | 31 | 9 | 17 |
| Nylon | 47 | 4 | 9 | 0 | 0 |

the end of the early graft period. Four of the nine grafts which failed spontaneously had experienced a severe early graft course. The other five had a moderately severe course. Of the 11 graft reactions, one had a severe course, six moderate, and four mild. In general, the clinical course of silk-sutured grafts is much more severe in the early graft period than that of the nylon-sutured grafts (Table 44).

The incidence of delayed reactions was somewhat greater in autografts than allografts, 29 vs 14% (Table 51). Similarly, delayed failure rate was higher in autografts. (Neither of these differences is significant.) This observation would mediate against the relationship of tissue incompatibility to the delayed graft reaction.

When grafted groups of rabbits are compared (Table 52), there is no appreciable difference between the in-strain and the cross-strain groups. (Group I vs II, and III vs IV are compatible.)

TABLE 51

COMPARISON OF THE INCIDENCE OF DELAYED GRAFT REACTIONS, ALLOGRAFTS VS AUTOGRAFTS

| Graft Group | No. Animals | Delayed Reactions | | Delayed Failures | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Allograft | 58 | 8 | 14 | 2 | 3 |
| Autograft | 41 | 12 | 29 | 7 | 17 |
| Total | 99 | 20 | 20 | 9 | 9 |

Of particular interest is the predominance of delayed graft reactions in albino rabbits, a ratio of 32 vs 3%. This ratio correlates closely with the abundance of both pathogenic and nonpathogenic bacteria on conjunctival culture of the albino rabbit in contrast to that of the pigmented rabbit. Likewise, the albino animal almost always demonstrates the nonpathogenic H. mimae and, frequently, moraxella, while the pigmented animal is virtually free of all bacteria.

In summary, of the variables evaluated in spontaneous delayed graft reactions, severity of structural change and prevalence of pathogenic and nonpathogenic bacteria appear to be significant, while tissue incompatibility appears to be unrelated to the reaction.

The exogenous stimulation experiments were designed to demonstrate that: (1) an exogenous stimulus can produce graft failure, (2) the degree of structural alteration

TABLE 52

OCCURRENCE OF DELAYED GRAFT REACTION BY GENETIC GROUP

| Experimental Group | Total Eyes | Delayed Reactions | | Delayed Failure | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| I | 35 | 11 | 31 | 5 | 14 |
| II | 25 | 8 | 32 | 3 | 12 |
| Total (albinos) | 60 | 19 | 32 | 8 | 13 |
| III | 18 | 0 | 0 | 0 | 0 |
| IV | 21 | 1 | 5 | 1 | 5 |
| Total (pigmented) | 39 | 1 | 3 | 1 | 3 |

TABLE 53

EFFECT OF STRUCTURAL CHANGE ON SEVERITY OF IMMUNOGENIC DELAYED GRAFT REACTION

| Structural Change | Total Animals | Infiltrative Change | Partial Opacity | Total Opacity | |
|---|---|---|---|---|---|
| | | | | No. | % |
| Allograft | | | | | |
| Absent (host) | 10 | 8 | 2 | 0 | 0 |
| Neovascularization | | | | | |
| Mild | 8 | 3 | 4 | 1 | 12 |
| Severe | 7 | 1 | 2 | 4* | 57 |
| Autograft | | | | | |
| Absent | 9 | 6 | 2 | 1 | 11 |
| Neovascularization | | | | | |
| Mild | 7 | 3 | 3 | 1 | 14 |
| Severe | 9 | 0 | 3 | 6* | 67 |

* One totally opaque allograft and one autograft developed buphthalmos following continuous topical BGG challenge.

of the host cornea will determine the severity of the inflammatory response, and (3) the host must demonstrate an adequate immune response to the challenging antigens for graft failure to occur.

In the initial experiment, the severity of the delayed graft reaction following topical BSA challenge was related to the degree of structural change within the host cornea (Table 53). Fifty-seven percent of allografts and 67% of autografts with severe structural change developed complete donor opacity following exogenous BSA challenge. Corneas demonstrating mild or absent neovascularization of the host rarely went on to complete opacification. Buphthalmos occurred following chronic exogenous stimulation. In this reaction, it would appear that an adequately prolonged iritis and trabeculitis must be produced before outflow channels are blocked and buphthalmos results. There was no apparent difference between allografts and autografts in their reaction to the exogenous stimulus.

TABLE 54

ANTI-BSA TITERS RELATED TO SEVERITY OF IMMUNOGENIC INFLAMMATION IN THE DONOR CORNEA

| | Antibody Titer Expressed in Diameter of Diffusion | | | | | |
|---|---|---|---|---|---|---|
| | 4 mm | 6 mm | 8 mm | 10 mm | 12 mm | 14 mm |
| Absent host vascularity | | | | | | |
| Infiltrative change | 1 | 1 | 3 | 6 | 3 | |
| Partial opacity | | | | 1 | 2 | 1 |
| Total opacity | | | | | | 1 |
| Mild neovascularization | | | | | | |
| Infiltrative change | 2 | 1 | 2 | 1 | | |
| Partial opacity | | 1 | 2 | 3 | 1 | |
| Total opacity | | | | | 1 | 1 |
| Severe neovascularization | | | | | | |
| Infiltrative change | 1 | | | | | |
| Partial opacity | 2 | 2 | | 1 | | |
| Total opacity | | 1 | 3 | 4 | 1 | 1 |

TABLE 55

EFFECT OF BGG CHALLENGE ON NORMAL AND GRAFTED EYES

| Structural Change | Total Animals | Limbal Hyperemia | Corneal Infiltrate | Partial Opacity |
|---|---|---|---|---|
| Normal | 14 | 14 | | |
| Absent neovascularization | 9 | 3 | 5 | 1 |
| Mild neovascularization | 5 | 1 | 3 | 1 |

In addition to structural alteration, reaction severity also depends upon the host ability to respond to an exogenous stimulus. In Table 54, antibody titers are compared with the severity of the donor response. In cases with absent or mild neovascularization of the host cornea, total opacification was producible only in animals demonstrating very high antibody titers (12 or 14 mm ID), while in severe disease, total opacity could be produced despite much lower titers.

The second group of exogenous stimulation experiments attempted to differentiate between structural predisposition of corneas with absent or mild host vascularity and a normal cornea. On BGG challenge, this group of grafted animals showed signs of clinical inflammation, corneal infiltrates, and anterior opacity. Normal eyes demonstrated only signs of conjunctival and limbal disease (Table 55).

This experiment serves to emphasize the effect of structural change on the predisposition to corneal inflammatory disease, since BGG is too large a molecule to produce change in the normal cornea.

## RESULTS

The delayed graft reaction in the rabbit, in contrast to that in man, originates exogenously and develops the corneal pattern of disease. Pathogenic or indigenous bacteria were recovered in every spontaneous reaction. However, immunogenic stimuli can also ignite the reaction, as the exogenous stimulation model demonstrated. However, with inflammatory resolution the rabbit donor cornea either clears or goes on to buphthalmos.

A majority of spontaneous delayed graft reactions occurred in the first two months following the end of the early graft period (between 75 and 135 days following surgery). As noted in the patient series, this period proximal to the early graft reaction exhibits the greatest degree of active structural alteration. OVP is increased in this period, while it tends to normalize with the passage of time. This is readily demonstrated clinically by the progressive involution of blood vessels in the host cornea with time.

Significant factors evaluated in the spontaneous delayed graft reaction included: (1) exogenous bacterial stimulation, (2) tissue incompatibility, and (3) the early graft variable, suture toxicity.

When pathogenic or indigenous bacteria were identified in delayed graft reactions, many more microbes were identified in the inflamed eye. This was particularly true in the case of indigenous bacteria, indicating a causal relationship.

The role of host response in the delayed graft reaction was demonstrated in the exogenous challenge experiments. If structure was normal, an animal required more immunity to produce a reaction. It seems likely that an adequate immune response must be present for a reaction to occur.

The potential role of tissue incompatibility as a factor in the experimental delayed graft reaction has been eliminated. As noted: (1) bacteria have been identified in the presence of spontaneous reactions, and (2) the incidence of delayed reactions is about the same in allografts and autografts (Table 52). The classic hypothesis that this reaction represents a delayed-onset tissue incompatibility reaction[1,2] was principally built upon analogy to vascular organ transplants such as the kidney, heart, and lung,[3-5] or to the second-set reaction.[6,7] In the former, inflammatory reactions frequently occur at intervals long after surgery and respond to immunosuppression.[8,9] In the latter, grafting of tissue at a later time from the original donor will produce a corneal reaction. Neither appears to apply in this case.

The cornea is unique in its dual characteristics of minimal antigenicity and avascularity, a combination which makes tissue incompatibility a minor factor in the early graft period and of questionable significance in the delayed reaction.

Suture toxicity, the most important factor in the early period, plays an indirect role in the delayed reaction. By producing a severe inflammatory response during the early period, suture toxicity results in severe structural changes which predisposes the eye to a delayed graft reaction. The degree of structural change produced by silk sutures was considerably greater than that demonstrated by nylon. Similarly, the occurrence of delayed reactions in silk-sutured animals was much greater than in nylon-sutured animals.

The role of structural alteration is extremely well demonstrated in the immunogenic stimulation model. With increasing severity of structural alteration, delayed graft reactions could be produced in animals with relatively low antibody titer. The pathogenesis of structural alteration allows for a much greater number of gamma globulin molecules to enter the cornea. Even though specific antibody titer is low, the total number of antibody molecules entering the cornea is adequate to effect an immunogenic inflammatory response.

In summary, the delayed graft reaction in the rabbit appears to be composed of: (1) stimuli in the exogenous environment, (2) an adequate host response, and (3) adequate

structural alteration in the host cornea. The effect of the early graft reaction on predisposition to subsequent delayed disease is mediated through structural alteration. Intrinsic tissue incompatibility plays no identifiable role in this reaction.

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## SUMMARY

These studies evaluate several factors which influence the outcome of a penetrating corneal graft. These factors include preoperative patient classification based on a combined clinical and morphologic system, preoperative protocols, donor cornea selection, the surgical procedure, the choice of suture, and postoperative management during the early and delayed graft reaction periods.

The long-term outcome for penetrating keratoplasty is promising. Our overall success rate for clear grafts is 72%. Including multiple procedures per eye, the success rate becomes 81%. With the optimal procedure, long-term success increases to 89% for cases and 91% for eyes.

Of greater importance is the functional result achieved in grafted eyes. We designated a visual acuity of $> 20/40$, usually with a corneal contact lens, as a good visual result. In more than 54% of all eyes treated, this result was achieved. Excluding cases with poor prognosis, more than 76% of eyes attained this level of visual acuity.

These studies illustrate that the penetrating keratoplasty is a practical restorative procedure for almost every vision-decreasing corneal problem.

## GLOSSARY

1. *Corneal graft (transplantation, keratoplasty)*—Replacement of diseased corneal tissue with viable nondiseased corneal tissue. In this study all grafting procedures were performed as penetrating keratoplasties utilizing allogeneic (homologous) donor corneal tissue.

2. *Corneal autograft*—A graft for which the donor cornea is taken from the patient's opposite eye.

3. *Corneal graft reaction*—An inflammatory reaction occurring in the host or donor cornea, or both, following corneal grafting and caused by a single inflammogenic stimulus or a combination of stimuli, e.g., suture toxicity, microbial toxicity.

4. *Corneal graft failure*—Nonclearing opacification of the donor cornea for any reason, e.g., inflammatory sequela, primary donor failure, tissue incompatibility reaction.

5. *Early graft reaction*—Corneal graft reaction occurring within the first 12 postoperative weeks in silk-sutured patients or 16 to 18 weeks in nylon-sutured patients.

6. *Delayed graft reaction*—Corneal graft reaction occurring after removal of sutures, approximately 12 to 16 weeks postoperatively.

7. *Inflammatory failure*—Opacification of the donor cornea resulting from effects of inflammation.

8. *Primary donor failure*—Immediate nonclearing opacification of the donor cornea after surgery resulting from nonviable or damaged donor endothelium.

9. *Clinical and morphologic classification of the host eye*—The system by which the host eye was evaluated preoperatively for varying degrees of structural change; the primary bases for this classification were presence or absence of corneal neovascularization and evidence of intraocular inflammation.

10. *Etiologic classification of the host eye*—Clinical diagnosis or identification of a specific causative agent.

11. *Suture toxicity*—A progressive inflammatory reaction presenting as suture tract infiltrate which is rapidly succeeded by neovascularization which in turn can culminate in graft failure. Suture toxicity was found to be a highly significant variable in this series.

12. *Microbial toxicity*—An inflammatory reaction which may be produced by pathogenic or indigenous (nonpathogenic) bacteria. The characteristic reaction produced by pathogenic bacteria presents as a suture tract abscess (Figs. 13-C, 21-G). Indigenous bacterial involvement presents as infiltrate along nlyon suture tracts. Viral infections (e.g., herpes simplex) occur as epithelial dendrites. Identification was by culture or by electron microscopy.

13. *Host immunologic classification*—Evaluation of host ability to respond to exogenous stimuli. Tests performed included: (1) protein electrophoresis, (2) qualitative immunoelectrophoresis, (3) quantitative IgG, IgA, IgM, and early IgG determination, and (4) $B_1C/B_1A$ evaluation.

14. *Tissue incompatibility (homograft) reaction*—An immunogenic host response to allogeneic donor corneal tissue. Identification of this reaction was achieved by exclusion of other inflammogenic variables. The reaction is characterized by a relatively uniform infiltration and neovascularization of donor tissue. It seems likely that the endothelial reaction described by Paufique and associates (Corneal Grafting. Paris, Masson, 1948) has been suppressed in our series by the use of corticosteroid.

15. *Successful graft*—A clear donor cornea throughout its entirety except suture tracts.

16. *Dependent noncorneal variables*—Introacular changes that have resulted from the keratoplasty procedure, e.g., glaucoma, retinal detachment.

17. *Independent noncorneal variables*—Intraocular changes that are unrelated to the

penetrating keratoplasty and most likely were pre-existing, e.g., macular degeneration, glaucoma.

18. *Long-term graft results*—Evaluation of graft success or failure after nine months or longer by morphologic, etiologic, and immunologic criteria.

19. *Case*—A single penetrating keratoplasty, e.g., one eye in this series received three keratoplasties and thereby is three *cases*.

20. *Eyes*—The number of individual eyes on which surgery was performed.

21. *Patients*—The number of individual patients on whom surgery was performed (12 patients had bilateral surgery).

22. *Structural alteration*—The permanent changes in tissue or in cellular function which result from adequately severe or prolonged inflammation and characterized by scarring and neovascularization. Eyes which demonstrate such changes show a marked predisposition to inflammatory recurrence.

23. *Socioeconomic factors*—The combined characteristics of an individual's social behavior, personal habits, and environment.

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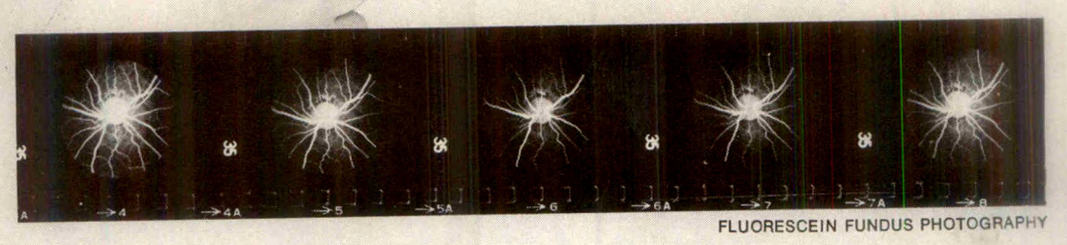
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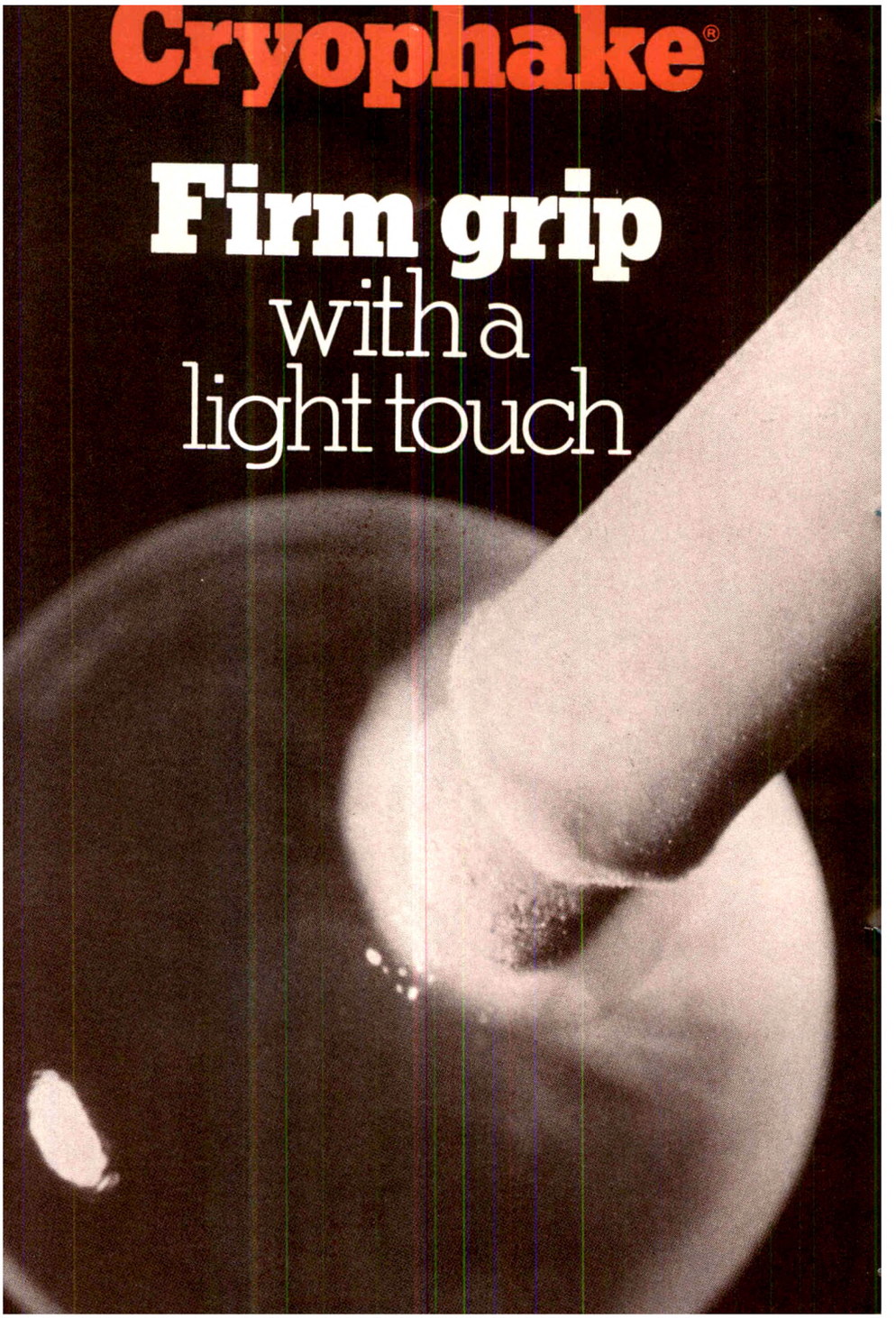

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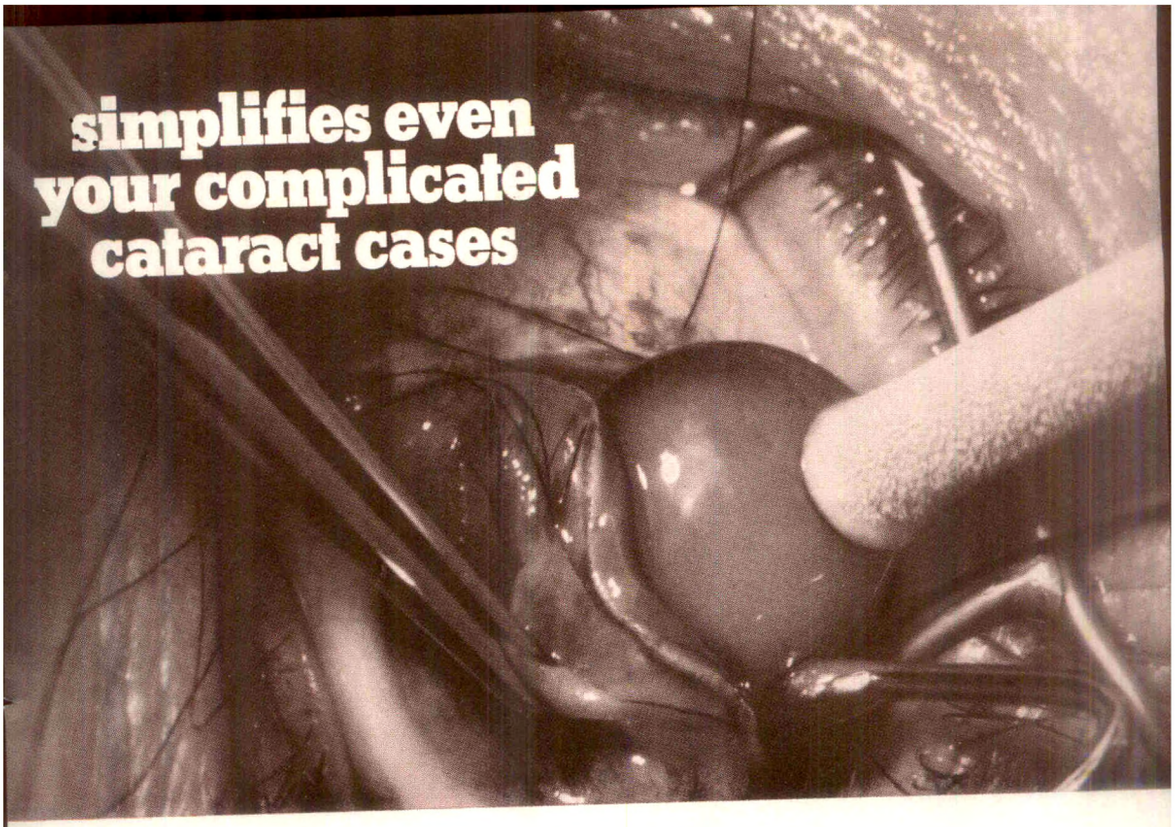
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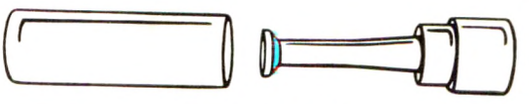
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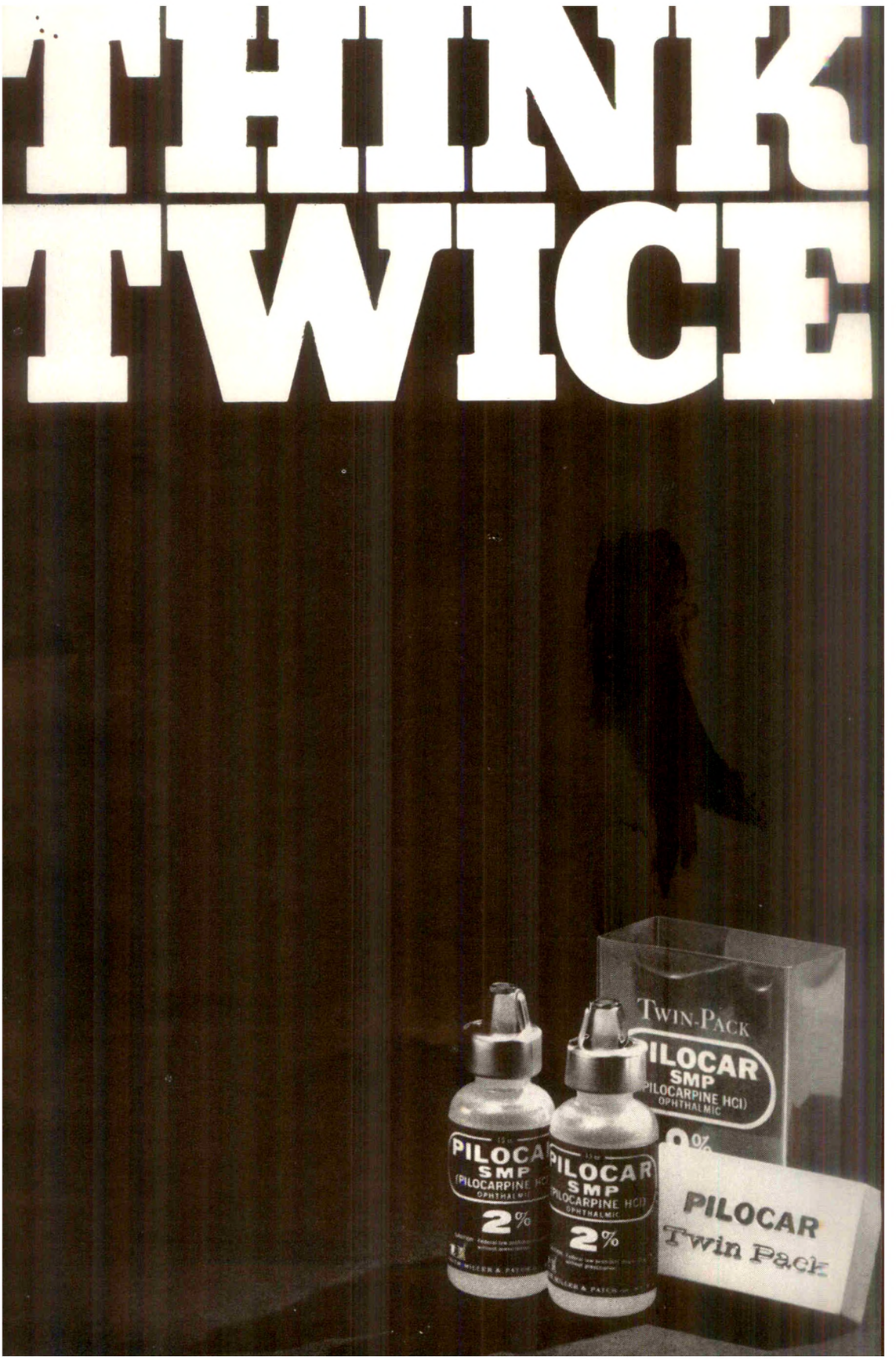
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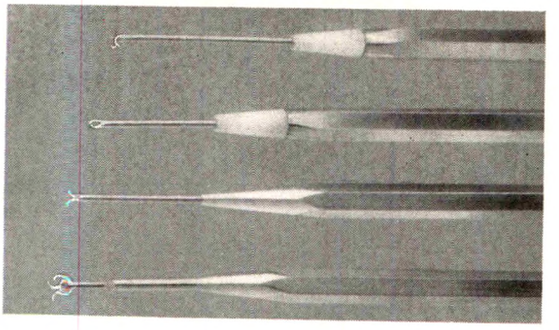
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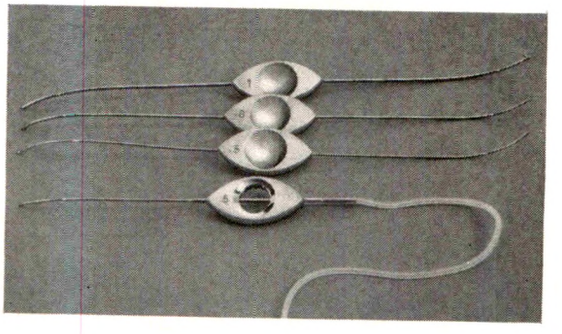
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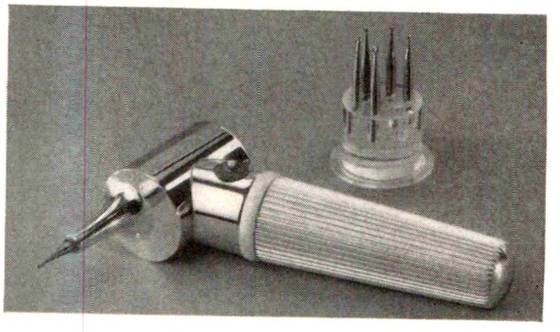
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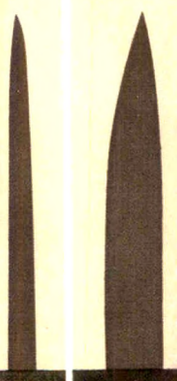
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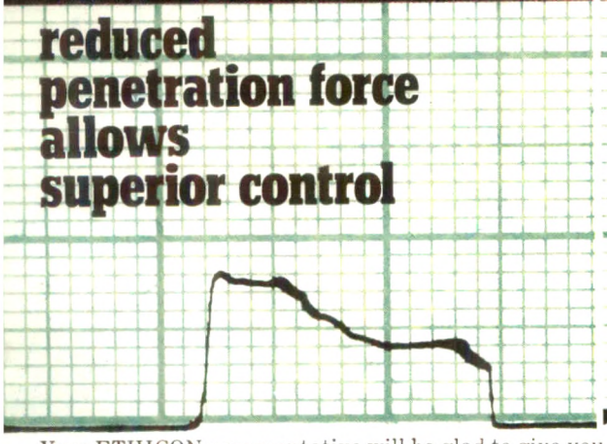
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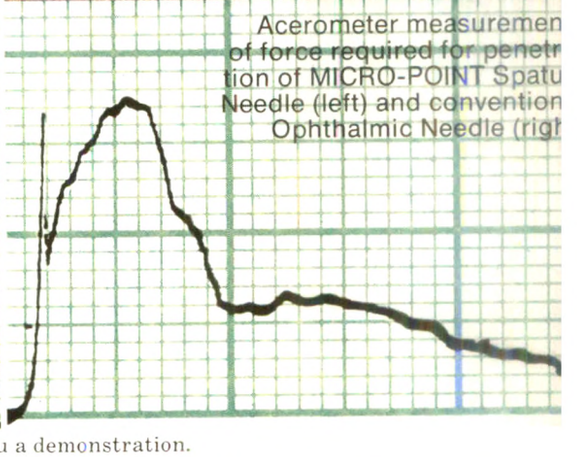
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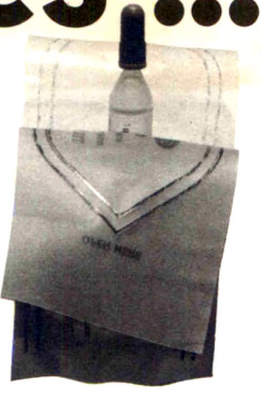
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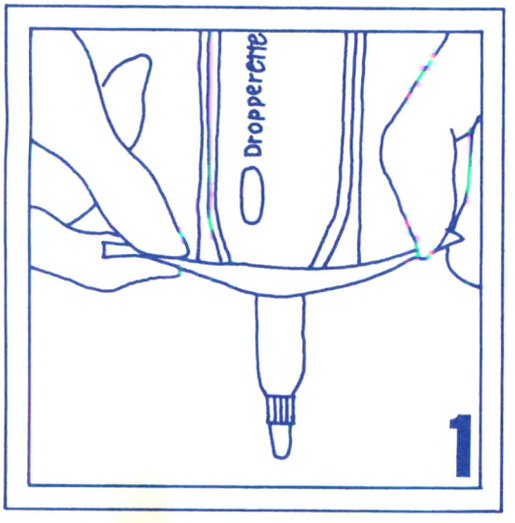

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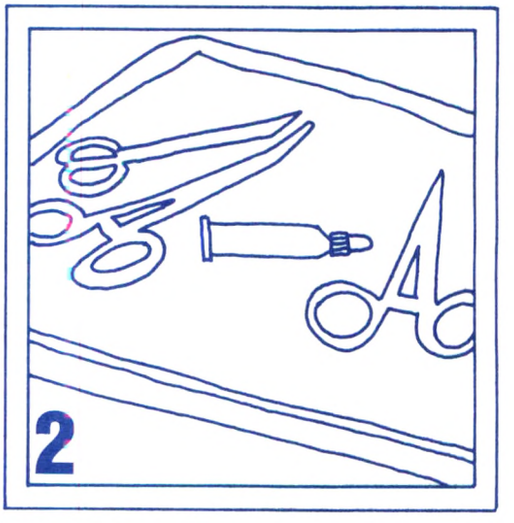
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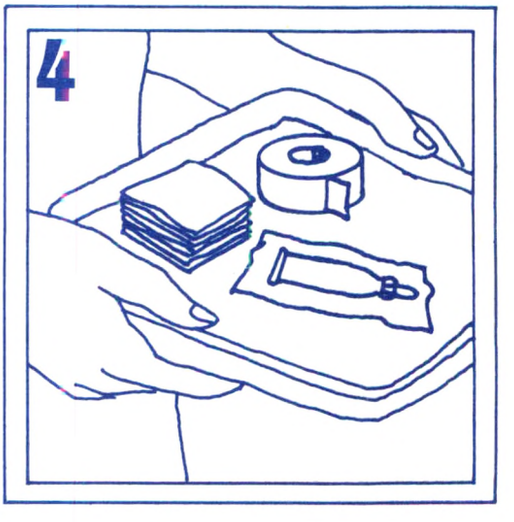
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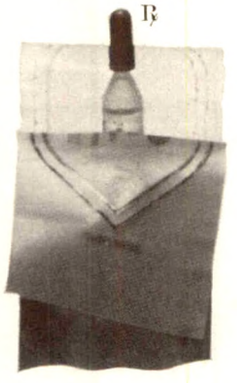



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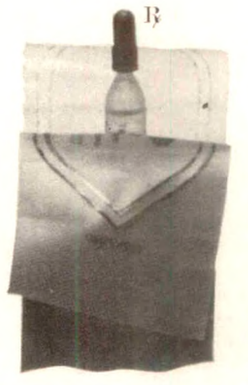
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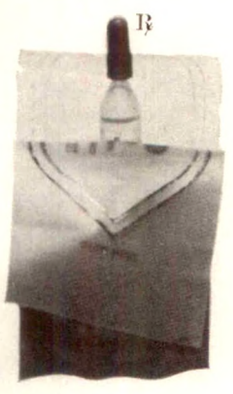
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(Atropine Sulfate)
0.5% 1% 2%



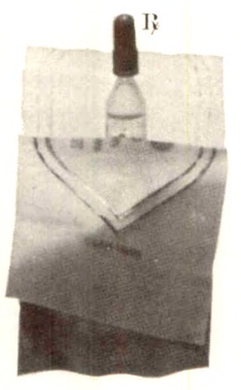
**EPINEPHRINE 1:1000 (1 cc.)**
(as the hydrochloride)



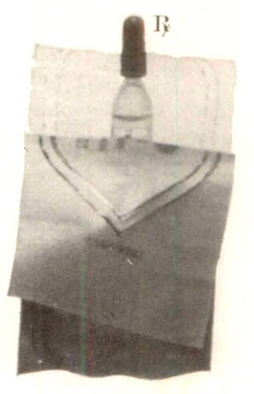
**FLUORESCEIN SODIUM 2% (1 cc.)**



**HOMATROPINE HBr (1 cc.)**
2% 5%



**PHENYLEPHRINE HCl 10% (1 cc.)**



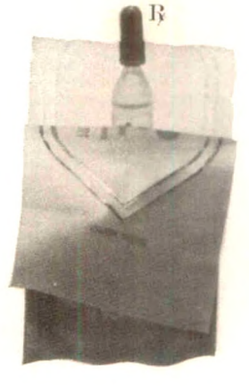
**PILOMIOTIN® (1 cc )**
(Pilocarpine HCl)
1% 2% 4%



**SULFACETAMIDE SODIUM 10% (1 cc.)**



**TETRACAINE HCl 0.5% (1 cc.)**



Cooper COOPER LABORATORIES, INC. WAYNE, NEW JERSEY 07470

**Composition:**

**Inflamase**

*Prednisolone Sodium Phosphate .....0.125%
(Equivalent to Prednisolone 0.1%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

**Inflamase Forte**

*Prednisolone Sodium Phosphate 1.0%
(Equivalent to Prednisolone 0.8%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

Prednisolone Sodium Phosphate is a water soluble inorganic ester of prednisolone. It is approximately 2,000 times as soluble in water at 25°C. as is hydrocortisone.

*Licensed under patent #3,134,718.

**Indications:** Inflamase and Inflamase Forte ophthalmic solutions may be used effectively in the following conditions of the anterior segment of the eye: superficial keratitis, including punctate epithelial lesions (Thygeson type), phlyctenular keratoconjunctivitis, and Sjogren's keratoconjunctivitis (with systemic steroids); deep keratitis, including interstitial or parenchymatous keratitis, acne rosacea, sclerosing keratitis; herpes zoster opthalmicus (do not use in herpes simplex); non-purulent conjunctivitis, including vernal, allergic, catarrhal; iridocyclitis; acute iritis; recurrent marginal ulceration, whether endogenous or due to atopic or contact allergies, or microbial allergy; corneal injuries, such as aseptic thermal, radiation, or chemical burns and corneal injuries following surgery or the penetration of foreign bodies; lid allergy; and non-purulent blepheritis, including catarrhal and allergic.

Inflamase and Inflamase Forte ophthalmic solutions have their principal effect on the anterior segment of the eye (cornea and the anterior uvea), with acute disorders responding more favorably than chronic disorders. Inflamase Forte 1% solution is recommended for moderate to severe inflammations particularly when rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

**Dosage:** Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops 2 to 4 times daily.

**Contraindications:** Contraindicated in acute herpes simplex, ocular tuberculosis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal diseases of the eye. Purulent conjunctivitis, purulent blepharitis, and infectious conditions are contraindications to the use of steroids.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

**Warning:** If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.

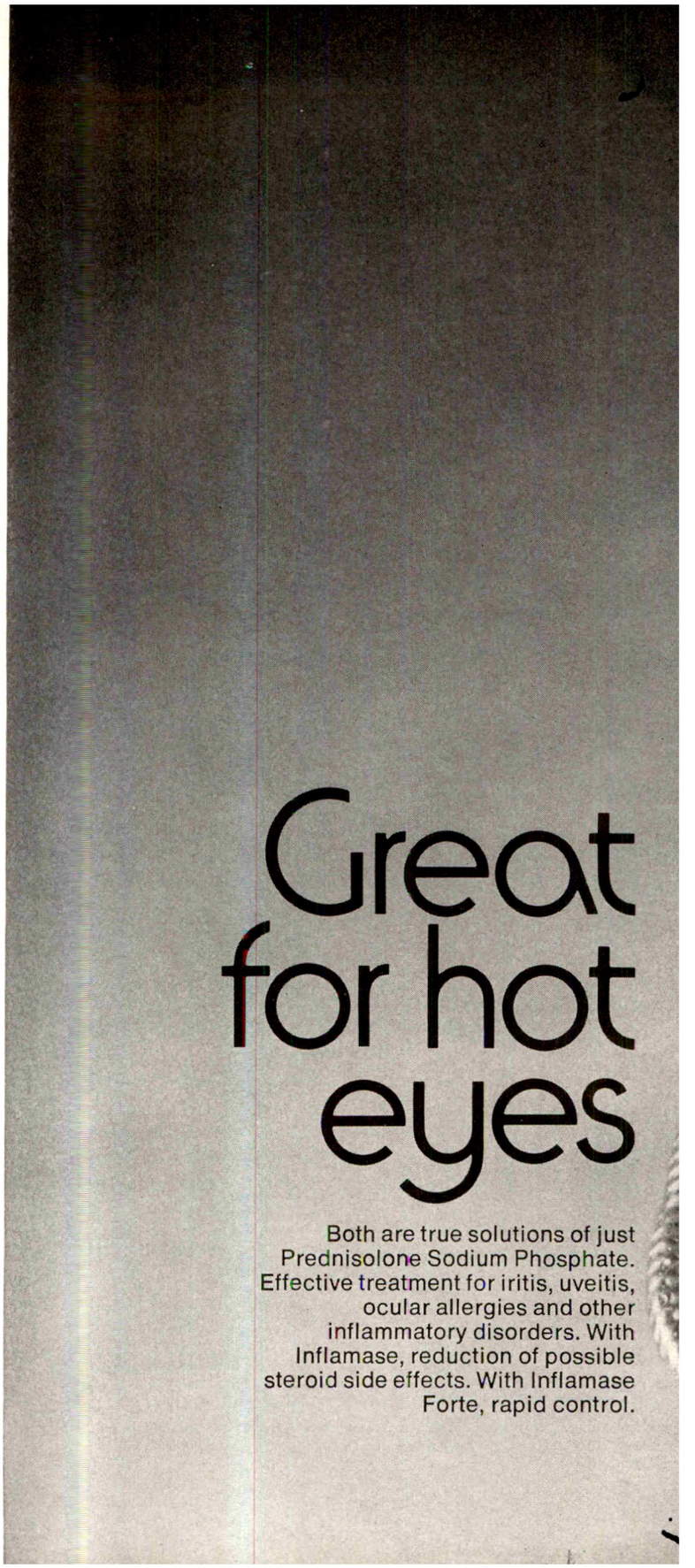
**How Supplied:** 5 cc plastic squeeze bottle with dropper tip. These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Store in cool place. Protect from light.

**Caution:** Federal law prohibits dispensing without prescription.

**Smith, Miller & Patch, Inc.**

401 Joyce Kilmer Avenue
New Brunswick, N.J. 08903



# Great for hot eyes

Both are true solutions of just Prednisolone Sodium Phosphate. Effective treatment for iritis, uveitis, ocular allergies and other inflammatory disorders. With Inflamase, reduction of possible steroid side effects. With Inflamase Forte, rapid control.




**Inflamase**
for most inflammations.

**Inflamase Forte**
for the tough ones.

# COVELLI CRYOEXTRACTOR

FOR CATARACTS

*Now available...*




## NO MORE ACCIDENTAL ADHESIONS!

ONCE YOU GRASP THE LENS, AT NO TIME DOES THE IRIS OR ANY OTHER TISSUE ADHERE TO THE PROBE, EVEN WHEN THERE IS DIRECT CONTACT!. THIS EXCEPTIONAL ADVANTAGE IS DUE TO ITS SPECIALLY DESIGNED TIP.

OTHER IMPORTANT ADVANTAGES:

- Thin tip (2.75 mm.) with special shape for better visibility.
- Light weight (11 g.) Just like your ball pen.
- Heat - resistant, so it can be autoclaved repeatedly.
- Durable, it can be used a great number of times.
- Rechargeable, uses gas *"FREON" 12; commercially available.
- Low price.

Ref. : Covelli B. Am. J. Ophth., 69:3, 1970
Presented at the VII Pan-Am. Congr. Ophth., Bogota, 1971

*Reg'd Trademark E. I. DuPont

F. D. Gillespie, M. D.
1205 Market Street
Parkersburg, West Virginia.

Please send me
ADDITIONAL LITERATURE

Name _____
Address _____
_____
_____



"to make it perfectly clear–"

# Neosporin®

## Ophthalmic Solution, Sterile

polymyxin B–neomycin–gramicidin

Each cc. contains: Aerosporin® brand Polymyxin B Sulfate 5000 units; Neomycin Sulfate 2.5 mg. (equivalent to 1.75 mg. of neomycin base); Gramicidin 0.025 mg., in aqueous saline solution isotonic with tears, containing the inactive ingredients alcohol (0.5%), propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride, and purified water (preservative: thimerosal 0.001%). Bottles of 10 cc. with sterile dropper.

## eradicates bacterial conjunctivitis and other eye infections due to susceptible organisms–

- highly effective against almost all pathogens which invade the eye, including *Pseudomonas* and *Staphylococcus aureus*
- bacterial resistance rarely develops on repeated or prolonged use
- low allergenicity
- also available: Neosporin® Ophthalmic Ointment—Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5000 units; Zinc Bacitracin 400 units; Neomycin Sulfate 5 mg. (equivalent to 3.5 mg. neomycin base) in special white petrolatum q.s. In ⅛ oz. tubes with ophthalmic tip.

*Precaution:* As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

*Contraindications:* This product is contraindicated for subconjunctival or intraocular injection, or for irrigation of fistulous tracts. This product is also contraindicated in those individuals who have shown hypersensitivity to any of its components.

Complete literature available on request from Professional Services Dept. PML.

Wellcome

**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

*THE TISSUE-FRIENDLY*

# SUPRAMID EXTRA®



**SUTURE.** Polyfilament but neither braided nor twisted. New cable-type construction with several strands enclosed in a perfectly smooth cover of the same material, gives great pliability and superior strength. Strong as steel wire, handles as silk. No stitch irritation, no growth of tissue into suture. Sizes 10-0 to 8.

**SPECIAL NEEDLES:** Our CT needle for cataracts (wire size 0.30mm, length 9mm), CA needle for corneal work (wire size 0.30mm, length 6mm), and EX needle for special keratoplasties (wire size 0.2mm, length 5mm), a flattened reverse cutting needle to prevent "leaking wounds," equal to the smallest hand made eyed needles No. 82F, **and finally the smallest spatula needle on the market, length 5 millimeters, wire size 0.2mm, double armed with 10-0, 9-0 and 8-0 black Supramid Extra. Code Nos. 2SC-100, 2SC-90 and 2SC-80.**

**A NEW PRODUCT:** Implants—Sleeves (Tubes) for preventing adhesions in Eye Muscle Surgery. Method development by Edward A. Dunlap, M.D. Reference: Dunlap, Edward A.: Plastic Implants in Muscle Surgery, Archives of Ophthalmology, 80: 249-257, August 1968.

**TUBING.** *Fully inert because it is made of the same material as the suture;
* Thinnest walls of any surgical tubing, fully transparent and can be *repeatedly* autoclaved;
* Most economical. It is in your interest to compare prices and quality.

**FOIL.** Excellent results with our suture created the demand for Foil for plastic and reconstructive surgery in such cases as orbital fractures, lid reconstruction, etc. Foil is chemically identical with the sutures, thus just as inert when buried in the tissue.

Available in thickness from 0.05mm to 2.00mm, in sheets 15 x 20cm.

Can be steam-autoclaved, cut to size, and carved to shapes and forms.

References: Merrill J. Reeh and James K. Tsujimura: Early Detection and Treatment of Blow-out Fractures of the Orbit, Am. Journal of Ophthalmology, 62: 79-82, 1966. Callahan, Alston: Reconstructive Surgery of the Eyelids and Ocular Adnexa. Aesculapius Publishing Co., Birmingham, Alabama, 1966. Cibis, Paul: Lid Reconstruction and Lifting with Fenestrated Supramid Supports. Klin. Monatsbl. Augenh., 112, 3, 1947. J. Barraquer—Z. Cuellar-Montoya: Keratoplasty: Superficial and Deep Corneal Sutures, Annal of Ophthalmology, 1:34-38, 1969. Mustarde, John C.; Jones, Lester T. and Callahan, Alston: Ophthalmic Plastic Surgery Up-To-Date. Aesculapius Publishing Co., Birmingham, Alabama, 1970.

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*Sole importer for USA, Canada, Mexico:*

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# Tillyer Topics



E. WILLIAM TILLYER

## Aspheric Cataract Lenses

Of all the work done in optics for the betterment of vision, perhaps the most spectacular is the development of aspheric cataract lenses. Nowhere can I recall such dramatic improvement in the quality of vision as that which occurs when properly developed aspheric curves are used in place of spherical curves in the aphakic patient's prescription.

The patient's reaction, of course, is the ultimate criterion. But the advantages of the aspheric curves can be proved mathematically.

For instance, a +14.00 sphere, if made up in a spherical curve with a —3.00 D inside curve, has the following Rx at 15mm away from the center of lens:

$$+14.16 = +2.14$$

The aspheric lens of the same power has an Rx at 15mm away from the center of:

$$+14.31 = -.75$$

This is quite a dramatic reduction in the marginal error. It is no wonder so many patients are extremely pleased with their new aspheric lenses!

But just being an aspheric lens does not make all the difference. One cannot use the same aspheric curve for all Rx's and still get these same results. The marginal effects of each power of sphere combined with each cylinder must be computed. Then a determination can be reached of the best aspheric curves for the individual power required.

We use 29 different base curves in the range from plus 8.00 D to plus 20.00 D. Only with this minimum can we achieve what we consider the ultimate results.

This seems like a lot of changes—more than one for every half diopter change in Rx power. But it gives the patient better vision every time.

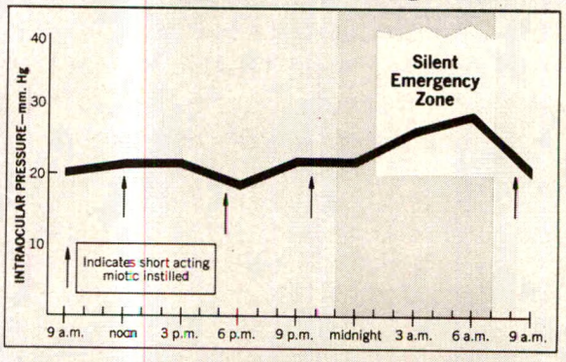
There are other areas where improvements have been made in lens design which are extremely important. But I, personally, still believe that none are as dramatic as the vision given the aphakic patient—by the use of a true aspheric series of cataract lenses.

AMERICAN OPTICAL
CORPORATION
Optical Products Division • Southbridge, Mass. 01550

# Not more potent, but longer acting*...

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

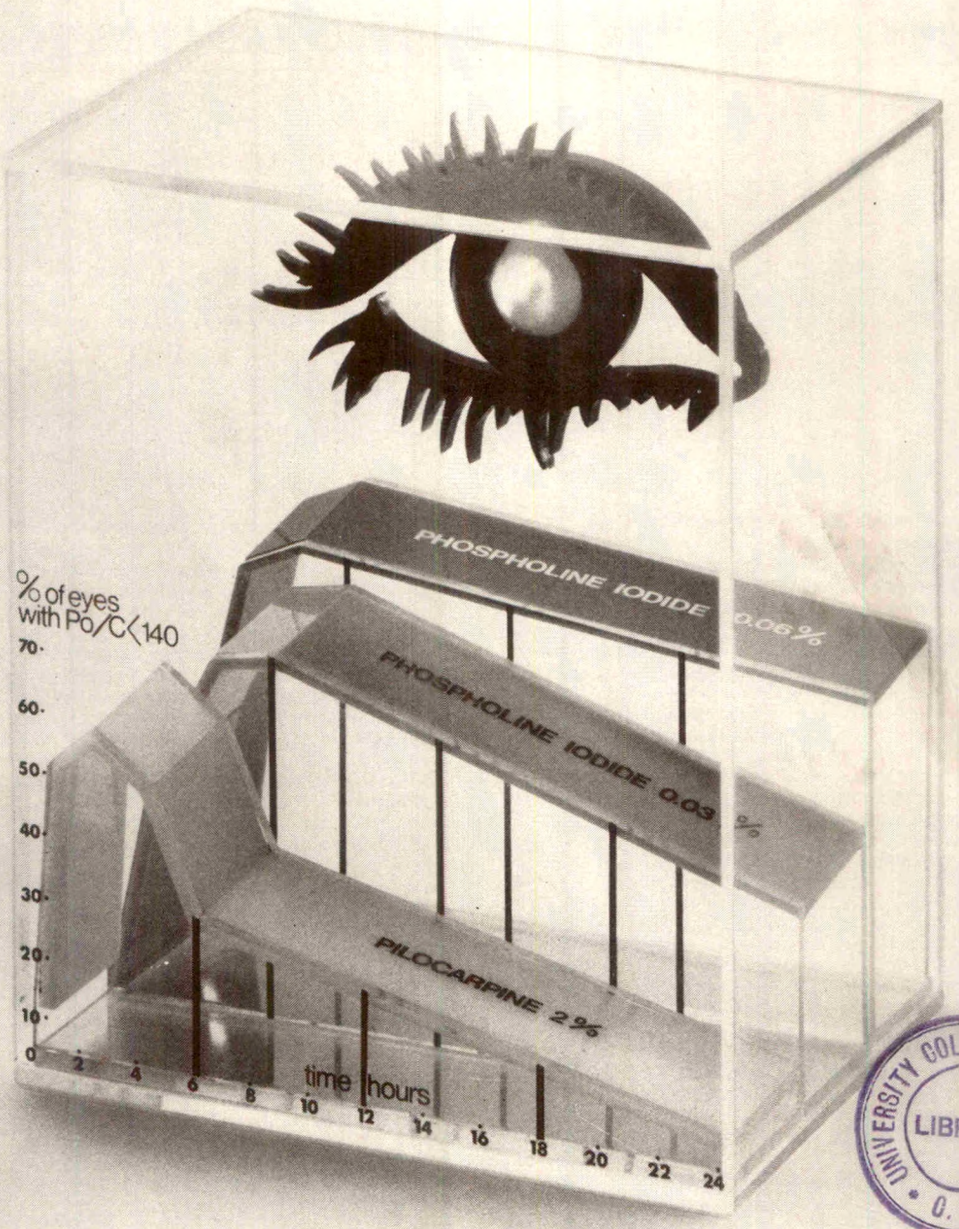



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25% —when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




UNIVERSITY COLLEGE OF MEDICINE
LIBRARY
O. U.

Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

for 24 hour control in chronic simple (open-angle) glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, brow-ache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

# *TRY OUR NEW MATH !*

## *2 + 10 + 15 =* **UNIKAT**

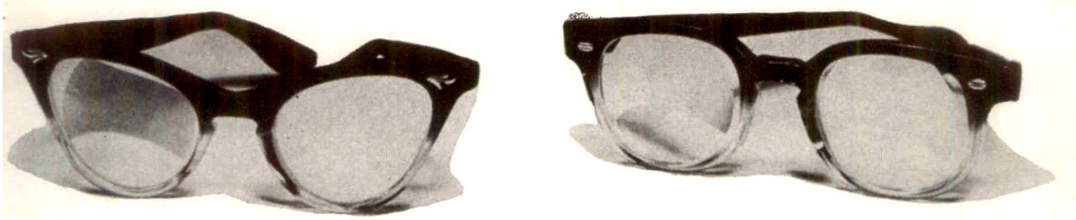
2 MODERN STYLES, for Men and Women

10 SIZES, from 42 to 48, for precise comfortable fitting

15 POWERS, from + 8.00 to + 15.50, in half-diopter steps, for better vision

All adds up to the best temporary cataract glasses !

## UNIKAT

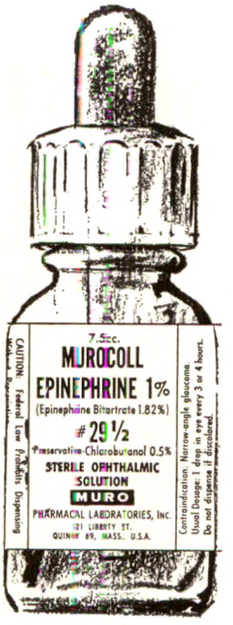


UNIVERSAL OPHTHALMIC PRODUCTS, INC

POST OFFICE BOX 3144
HOUSTON, TEXAS 77001

# MUROCOLL EPINEPHRINE 1%

**As (L-Epinephrine Bitartrate 1.82%)** **PRODUCT #29½**




- Effective in maintaining lowered intraocular pressure in certain cases of open angle glaucoma by reducing the rate of aqueous formation.
- Improves the facility of outflow after prolonged therapy in more than 50% of eyes with open angle glaucoma.*
- Aids in breaking posterior synechiae in uveitis.

Murocoll Epinephrine 1% (as Bitartrate 1.82%) with Chlorobutanol 0.5% as a preservative and bacteriostatic agent is also available as Murocoll Epinephrine 2% (as Bitartrate 3.64%), Product #29.

Both solutions also have Sodium Bisulfite as preservative; Sodium Chloride and distilled water as inactive ingredients.

Above solutions are contraindicated in narrow angle glaucoma. Use with caution in presence of hypertension.

Available: 7.5 cc. glass bottle with plastic dropper. ℞ only

Patient does not have to refrigerate above solutions.

Complete Ophthalmological Formulary Available On Request

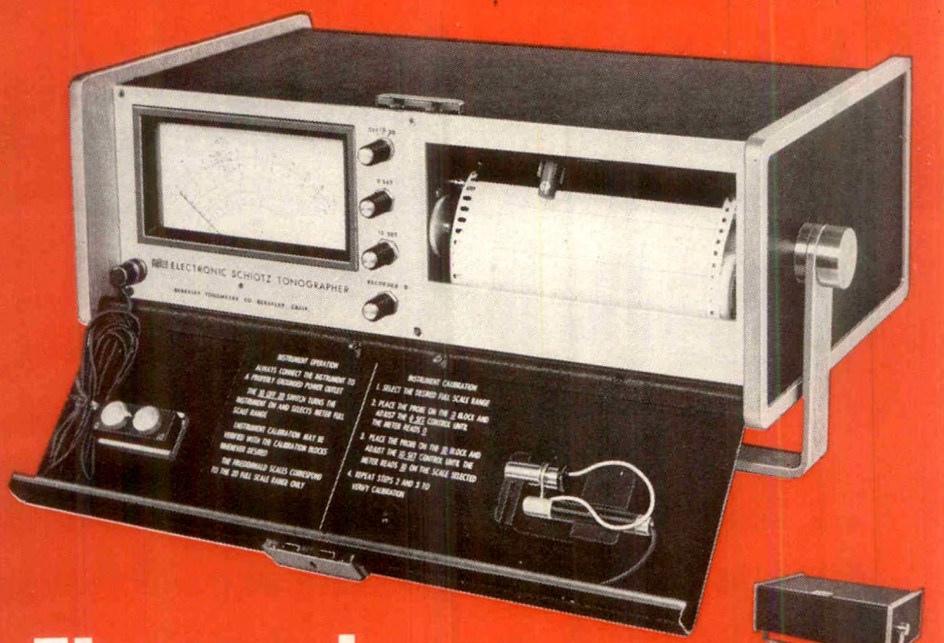
Originators of Stabilized Epinephrine Collyria

*BECKER ET AL. TR. SEC. A.M.A. 188, 1961

Muro preparations are available to all pharmacies and hospitals through their drug wholesaler, or may be obtained directly from our laboratories by indicating their usual source of supply.

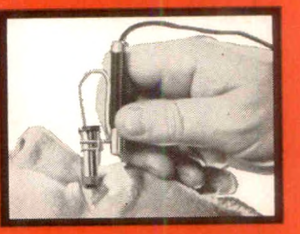
**MURO PHARMACAL LABORATORIES**

**121 Liberty Street — Quincy, Mass., U.S.A. 02169 — Area Code 617 - 479-2680**




# Electronic SCHIOTZ TONOGRAPHER

## TONOMETER & RECORDER



Continuous recording or individual record form. Records each eye in a different color with no-mess cartridge pens. ☐ Deluxe, long-scale meter with integral Friedenwald regression scales. Tungsten alloy weights. ☐ Solid-state electronics. Epoxy-glass printed circuitry. Micro-finished probe surfaces. ☐ Compact, lightweight. Power cord, footswitch, spare pens, calibration standards enclosed. ☐ Inkless recording without the expense of heat-sensitive paper.

**BERKELEY BIO-ENGINEERING, INC.** "AJO"

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☐ Please send me more information on the new 720 Tonographer.

Name

Address

City State Zip Phone

# THE 10 MOS
# QUESTIONS ABOU

## THE QUESTIONS

1. What makes PHOTOGRAY lenses work?
2. How fast do PHOTOGRAY lenses change?
3. Will the darkening-fading process wear out?
4. Do PHOTOGRAY lenses need breaking in?
5. Can PHOTOGRAY lenses be hardened or toughened?
6. How do PHOTOGRAY lenses work in a car?
7. In what types of lenses is PHOTOGRAY glass available?
8. Is the darkening-fading process comfortable to the wearer?
9. Do PHOTOGRAY glasses have a residual tint indoors?
10. Will PHOTOGRAY glass be available in a darker sunglass version?

**Note:** If you get asked other questions by your patients about PHOTOGRAY glasses that you think would be of broad interest, please send them to us. When we get enough new ones, we'll answer them in another ad.

If you'd like complete technical information on PHOTOGRAY lenses, just write to: Corning Optical Products Dept., Corning, New York 14830.

# FTEN ASKED
# HOTOGRAY® LENSES.

## THE ANSWERS

1. PHOTOGRAY lenses are photochromic: sensitive to ultraviolet light. When sunlight strikes them, invisible microcrystals of silver halide become darkened. When the light is removed, the crystals clear again.
2. Quite rapidly. In 60 seconds the lens is 75% darkened by sunlight and virtually fully darkened in 5 minutes. Removed from sunlight the lens clears half way in 5 minutes and 75% in 20 minutes. At their darkest, PHOTOGRAY lenses have a light transmittance of 45%. When clearest they have a light transmittance of 85%.
3. No. The photochromic reaction is locked into the composition of the glass and is completely reversible. It will keep performing for a lifetime without changing its characteristics.
4. Yes. Several complete darken-fade cycles are needed to bring PHOTOGRAY lenses up to their normal operating performance.
5. Yes, Most definitely. PHOTOGRAY lenses can be heat-treated or tempered. The tempering time is slightly different from that needed for clear lenses. Corning publishes heat-treating tables that give settings for the more popular units available.
6. Not too well. The window glass will screen out a lot of the ultraviolet light which activates the photochromic property of the lenses. This keeps the glass from darkening as fully as when it is exposed to direct sunlight.
7. PHOTOGRAY lenses come in a full range of sizes—in both single-vision and 1 piece multi-focal types.
8. Yes. The process, while quite rapid, is gradual enough to be imperceptible to the wearer. This, combined with the protection given by the darkened glass, is why PHOTOGRAY is known as the "comfort glass".
9. Yes. It's a very light, hardly noticeable tint.
10. Yes. Corning is currently in the final stages of developing a sunglass companion to PHOTOGRAY glass. Called PHOTOSUN™ glass, it's a true variable sunglass. PHOTOSUN lenses will be ready for introduction shortly.

CORNING
OPTICAL PRODUCTS

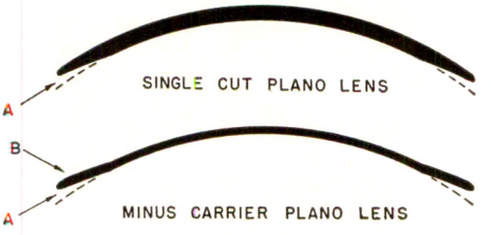


# THE ULTRA-THIN MINUS CARRIER CONTACT LENS

A vexing fitting problem is the low-riding lens which does not move enough as the patient blinks, resulting in tear stasis and edema under the lens apex. This problem is more prevalent with the use of small thin lenses today, since there is less lid action exerted on them; thus less movement. It is most common with plus and low-minus (under −3.00) single-cut lenses, since their thickness and consequent weight pulls them down. Also, the steep outside radius minimizes the upward pull of the lids. The partial blinking patient has the greatest problem with such low-riding lenses, since his lids may not come down far enough to move the lenses, or may make just enough contact to force the lenses down even farther.

Past solutions to the problem have been: (1) "Blink training"; (2) Larger lens diameter, so that the lens edge would be held up under the upper lid, so that even slight blink action would give more lens movement and tear interchange. However, often neither measure was successful and lens wear was curtailed or discontinued.

The *ultra-thin MINUS CARRIER LENS* offers new hope for these patients. It can be made *thinner* than single-cut lenses, since plastic removed from the posterior surface by peripheral curves at "A", which requires increased center thickness in a single-cut lens, is instead replaced at the anterior periphery of the MINUS CARRIER LENS at "B" by using a *flat carrier curve* which is parallel to or even flatter than the posterior peripheral curve. Thus, *no increase* in center thickness is needed.




The MINUS CARRIER LENS attacks the problem of low riding in two ways: (1) Being *thinner and lighter,* there is less gravitational pull and better centering; (2) The *flat anterior periphery* provides more upward lid pull and lens movement.

This lens can be fitted using the small thin lens technique, or as a larger diameter lens. As it is thinner and tends to be tighter, the preferred fit is as a small (7.8 to 8.8 mm) intra-palpebral fissure lens, free of the upper lid except during the blink. Due to its *flat anterior periphery,* even a partial blink will pick up the lens if the lid comes down several millimeters over the lens edge. If it still rides too low, or if the blink is too slight to pick up the lens, a larger diameter MINUS CARRIER LENS that positions under the upper lid at all times should provide sufficient tear interchange, even with minimal blink action.

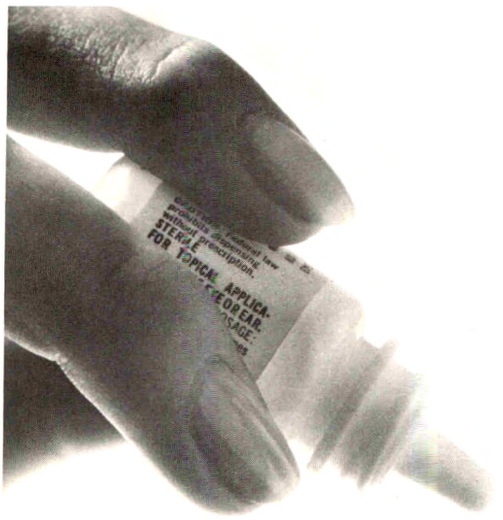
STANLEY GORDON, *President*

GORDON CONTACT LENSES INC.
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Most ophthalmic solutions start out sterile. But the OCUMETER® helps this one stay that way.
OCUMETER helps steroid solution stay sterile by eliminating a major cause of contamination —the eye dropper. Sterile, highly stable
Ophthalmic Solution
DECADRON®
Phosphate
(Dexamethasone Sodium Phosphate|MSD)
0.1% Dexamethasone Phosphate Equivalent
for mild acute iritis and nonpurulent conjunctivitis
For prescribing information, please see next page.

## for mild acute iritis and nonpurulent conjunctivitis




Not all steroid ophthalmic solutions stay sterile during the days and weeks of therapy. But this one is more apt to—Ophthalmic Solution DECADRON Phosphate (Dexamethasone Sodium Phosphate, MSD) in the OCUMETER® eliminates a common source of contamination—the eye dropper.

*Uniform dosage, drop after drop*

Each drop of Ophthalmic Solution DECADRON Phosphate contains the same dosage of steroid. And, with a gentle squeeze, the OCUMETER measures out one drop at a time. So your patient can conveniently get the steroid dose you want her to have, wherever she is.

Each cc. contains dexamethasone sodium phosphate equivalent to 1 mg. (0.1%) dexamethasone phosphate. Also available as DECADRON® Phosphate Ophthalmic Ointment (0.05%); and as NeoDECADRON® Ophthalmic Solution containing dexamethasone sodium phosphate equivalent to 1 mg. (0.1%) dexamethasone phosphate and neomycin sulfate equivalent to 3.5 mg. neomycin base in each cc.; and NeoDECADRON® Ophthalmic Ointment, containing dexamethasone sodium phosphate equivalent to 0.5 mg. (0.05%) dexamethasone phosphate and neomycin sulfate equivalent to 3.5 mg. neomycin base per gram.

Sterile, highly stable
Ophthalmic Solution
**DECADRON®** Phosphate
(Dexamethasone Sodium
Phosphate|MSD)

CONTRAINDICATIONS: DECADRON and NeoDECADRON should not be used in the presence of infectious tuberculous lesions of the eye, chickenpox, early acute herpes simplex, vaccinia, the early acute stages of most viral diseases of the cornea and conjunctiva, acute purulent untreated infections of the conjunctiva and lids, suspected ocular or aural fungal infection, perforated ear drum. Sensitivity to components is also a contraindication.

PRECAUTIONS: DECADRON: Like all adrenal corticosteroids, may sometimes mask, activate, or enhance incipient infection. Whenever possibility of infection exists, suitable antibiotic agents or a steroid-antibiotic preparation (such as NeoDECADRON) should be considered. If infections do not respond promptly, therapy should be discontinued until the infection has been adequately controlled by other measures.

Systemic side effects may occur with extensive use of steroids. Rarely, ocular herpes simplex has been reported in patients receiving adrenocortical steroids systemically or locally in the eye for other conditions.

As with other corticosteroids, increased intraocular tension can follow extended local use (1-2 weeks or more) of dexamethasone sodium phosphate. Since increased intraocular tension can lead to loss of vision, this possibility should be kept in mind and topical administration used only under adequate tonometric supervision, particularly in patients known to have glaucoma, or whose family history includes glaucoma.

In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. Reports in the literature indicate that, rarely, protracted use of topical corticosteroids in the eye may be associated with the development of posterior subcapsular cataracts. Hereditary and degenerative eye diseases in general do not show any response to treatment with these preparations.

Stubborn cases of anterior segment eye disease may require systemic adrenocortical hormone therapy. When the deeper ocular structures are involved, systemic therapy is necessary.

NeoDECADRON: A few individuals may be sensitive to one or more of the components of NeoDECADRON. If any reaction indicating sensitivity is observed, discontinue use. Sensitivity to neomycin may occasionally develop, especially when it is applied to abraded skin. Some reports in the current literature point to an increase in the number of persons sensitive to neomycin.

Use of any antibiotic agent may result in overgrowth of fungi or other organisms not susceptible to the antibiotic, necessitating prompt medical attention for such new infections.

As the safety of topical steroids during pregnancy has not been confirmed, they should not be used for extended periods during pregnancy.

**For more detailed information, consult your MSD Representative or see the Direction Circular. Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa. 19486**

**MSD** MERCK SHARP & DOHME




# BY ALL MEANS!

Armorlite originated the world's first hard resin lenses in 1947, and has been perfecting them ever since. We make more types of these modern lenses than any one else, and they have a reputation for unsurpassed quality. We make only hard resin lenses and we do it in earnest; they are not a side-line with us.

When you think patient care and protection, think Armorlites, by all means.

**ARMORLITE, INC.**

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**Caution:** Federal law prohibits dispensing without prescription.

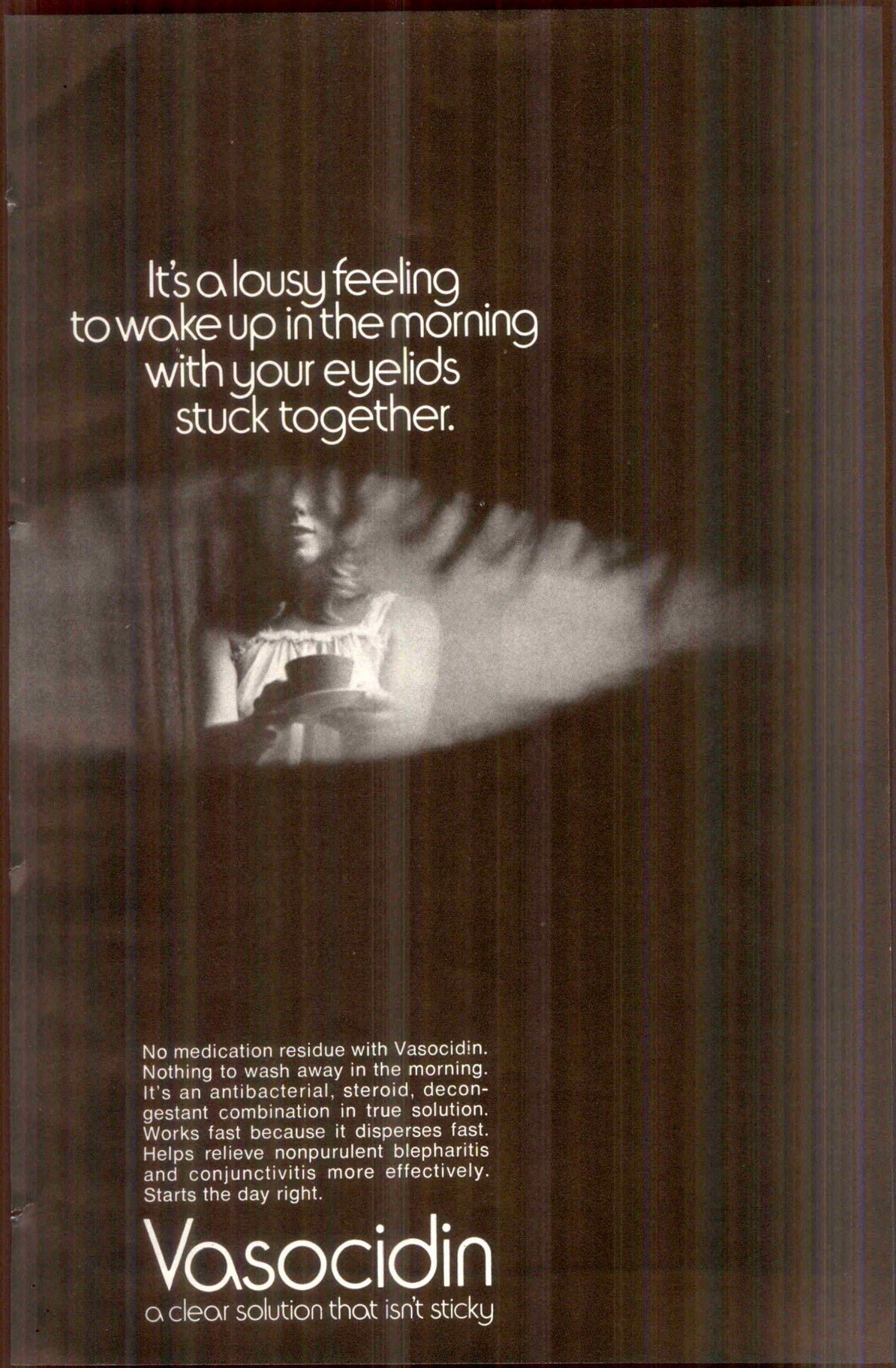
**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

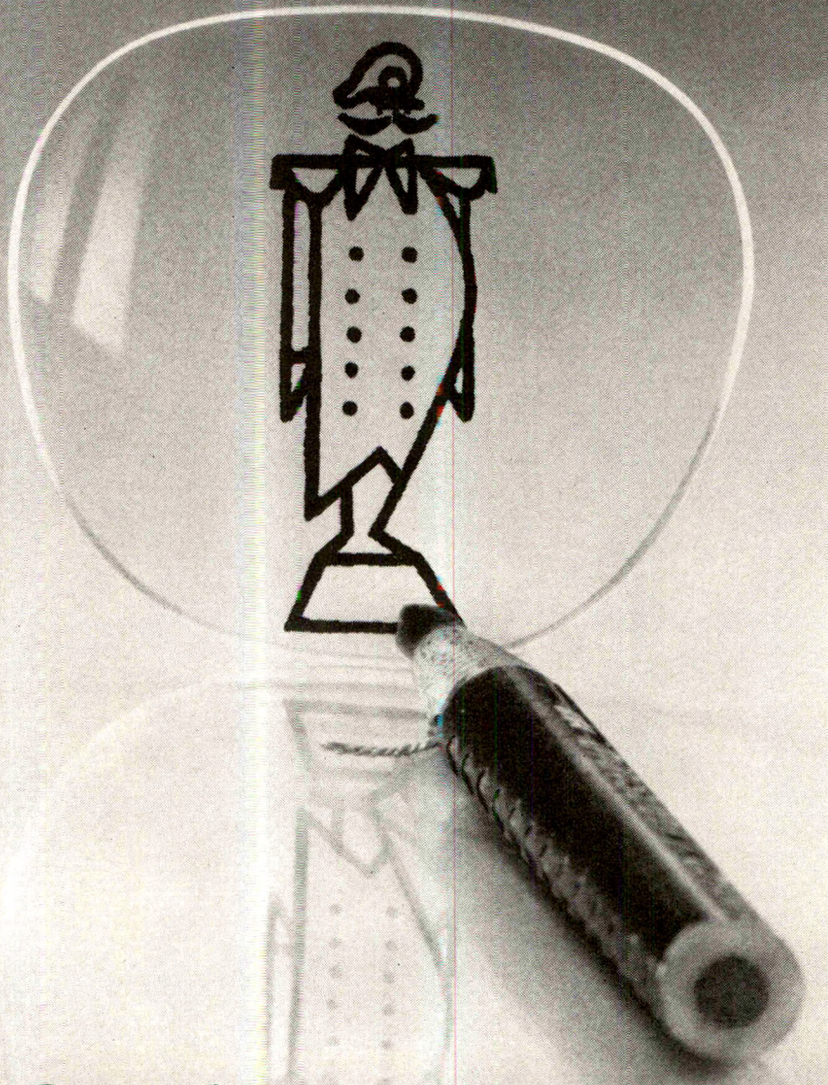
Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902


It's a lousy feeling
to wake up in the morning
with your eyelids
stuck together.
No medication residue with Vasocidin.
Nothing to wash away in the morning.
It's an antibacterial, steroid, decon-
gestant combination in true solution.
Works fast because it disperses fast.
Helps relieve nonpurulent blepharitis
and conjunctivitis more effectively.
Starts the day right.
Vasocidin
a clear solution that isn't sticky

# It's what you expect from us and what your patients expect from you.



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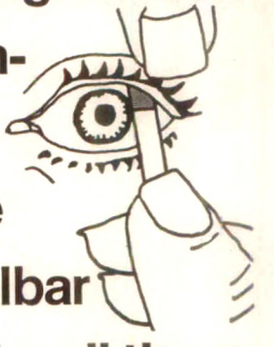
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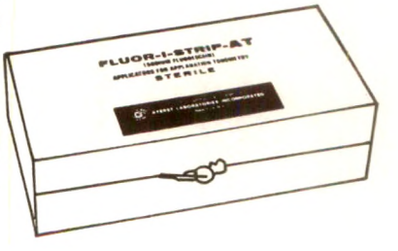


**When fitting contact lenses: to guard against the risk of infection inherent in the use of sodium fluorescein solutions, stain eyes with sterile Fluor-I-Strip-A.T. No excess fluorescein to stain the patient's face or clothing...water-proof grip to prevent staining of your fingers. Simply retract upper lid, apply dry orange tip of flexible applicator to the bulbar conjunctiva at the temporal side. For all these benefits: Specify Ayerst**





**FLUOR-I-STRIP®-A.T. (sodium fluorescein)**
**STERILE OPHTHALMIC APPLICATORS.**




*Each applicator contains* not less than 1.0 mg. sodium fluorescein —provided by precise impregnation with a solution of sodium fluorescein and 0.5% chlorobutanol (chloral derivative), polysorbate 80, boric acid, potassium chloride, and sodium carbonate. *Supplied:* No. 1048—Boxes of 100 envelopes, each envelope containing 2 firm sterile applicators—one for each eye.

OPHTHALMOS DIVISION

The Ophthalmos Division
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RLI

*RLI...has a contact lens protection program that has been thoroughly tested for 10 years...*

# NOW PROTECTS ALL "SOFT" CONTACT LENSES

RLI began preparations for the new soft contact lens years ago. Yes, that's right! RLI's regular contact lens protection program has been years ahead of its time. Our program has been thoroughly and successfully tested by the ophthalmic profession for ten years. This is your assurance of simplicity, reliability and integrity for you and your contact lens patients. Its many easy operating features, low premium cost, the highly effective recall system are immediately adaptable to the new soft contact lens situation.

We have made one significant change for soft contact lens wearers. RLI has strengthened the automatic recall system by adding a **six month recall** regardless of the term of the patient's policy. This means that your soft contact lens patients will receive a reminder to have their eyes examined and/or lens inspected **every six months.** This six month recall for soft contact lens wearers will be available through both our regular, and the Rx 6/12 laboratory programs.

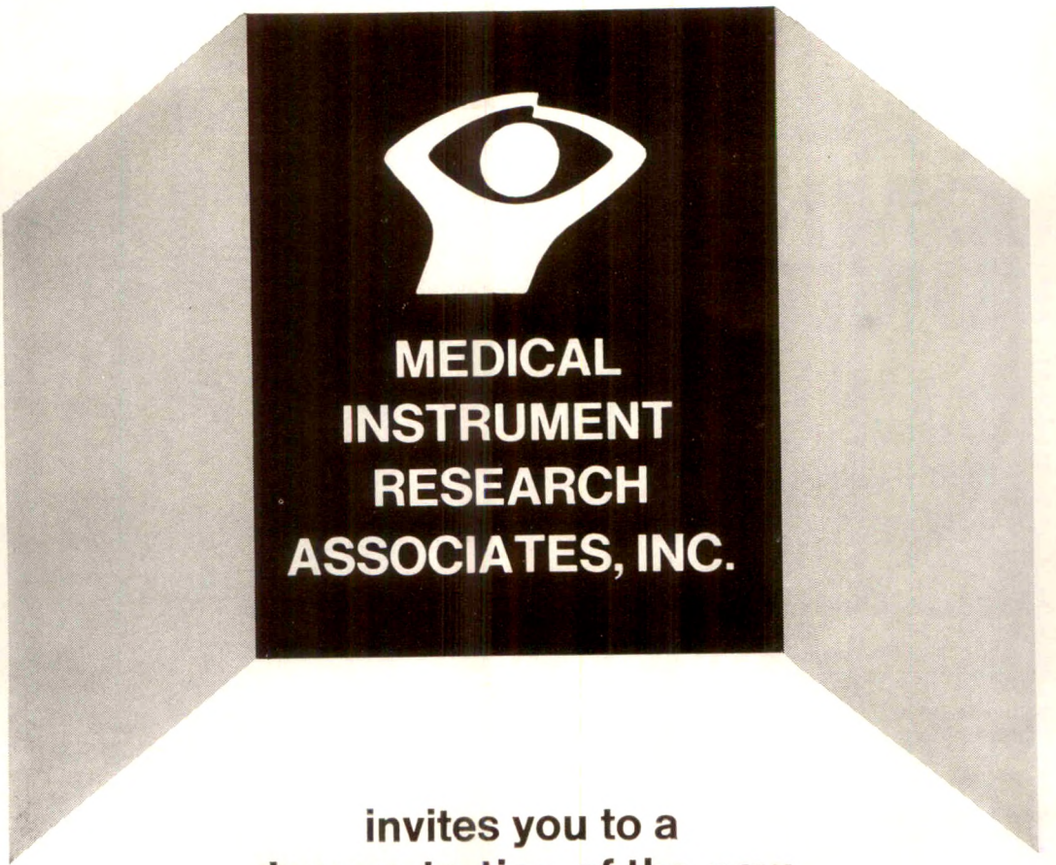
For further information about RLI's regular and soft contact lens insurance program, contact RLI today!

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- ARGON LASER COAGULATOR
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## A complete examination center in one compact modular unit.

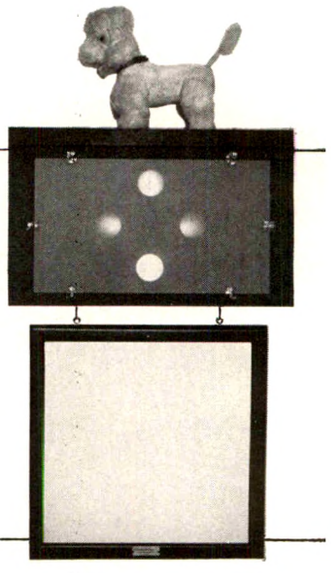
# DA-LAUR OMNIBUS UNITS

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*The most sophisticated ophthalmic control unit available today. Lets you conduct the entire examination from your chair by remote control.*

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**ANIMATED PUPPY UNIT**
maintains fixation during examination. Illuminated puppy's motion and bark keep children attentively fixing. Unit has standard adult white fixation light, changing color fixation light, and Worth 4-dot test — each with its own control switch. Shown with optional projector screen.

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*Designed by ophthalmologists for ophthalmologists®*

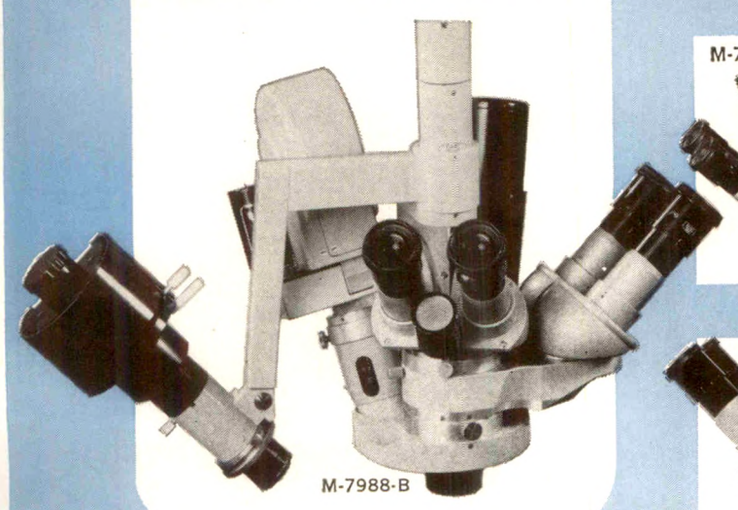
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*An Urban* modified Zeiss-Barraquer or Cine-Barraquer microscope . . .*

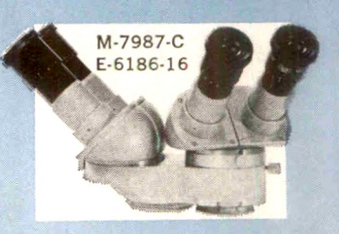
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*as used by Dr. B. E. Cohan, University of Michigan*










**For Surgeon and Assistant:**

- Provides two binoculars (M-7988-B)
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- Wide field eyepieces
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- Illumination: both homogeneous & slit
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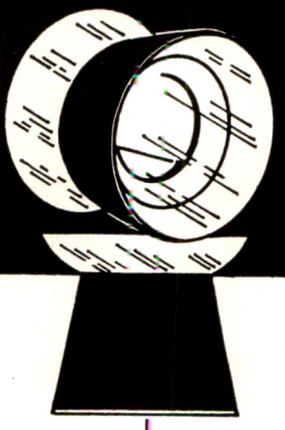
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# GONIO-GEL



A STERILE GEL OF METHYLCELLULOSE 4000 cps 2.5%
Preservatives: Methylparaben and Propylparaben

## VALUABLE FOR BONDING OF GONIOSCOPIC PRISMS TO THE CORNEA

- Simplifies gonioscopy in upright and recumbent positions
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- Helps maintain a tight lens fit
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Apply small amount of Gel to inner surface of Gonio lens.
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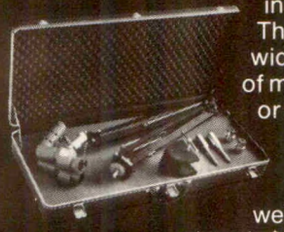
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# Born free

Like trend-setting CM-II, the new Mentor* CM-III Portable Operating Microscope gives total freedom to the surgeon—freedom to swing the microscope in when he wants it, out when he doesn't, freedom to turn away momentarily, freedom to carry it anywhere and set it up quickly, freedom from wearing or holding any equipment.

What's new is CM-III's steadiness. We have entirely redesigned the arm, pivot, and clamp for firmer, smoother action. When you swing it back in you return to the same focus, same angle, and same field of view without readjustment. (It's parafocal.) The maneuvering handles are sterilizable.

And the coaxial light source. The neat pool of light makes finding the subject much easier, then illuminates it at an intensity of 600 foot-candles. The optics present a bright, wide, flat field at your choice of magnification—7X, 10.5X, or 14X.



The price of the CM-III, complete with attractive, lightweight carrying case, is only $1060. Let us send you complete information. Mentor Division, Codman & Shurtleff, Inc., Randolph, Mass. 02368.

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# Invisible bifocals are no longer a novelty, so when you prescribe them . . . specify YOUNGERS, and here's why!

Younger Seamless Lenses were introduced almost fifteen years ago and have been actively promoted ever since. When a sufficient market for this type of lens was created, other invisible bifocals were introduced. Most are based on the somewhat dubious assumption that the human eye can effortlessly seek a "graduated" power which would give adequate vision at a predetermined distance.

Fine in theory — but in actual practice, certain optical aberrations are thus introduced, such as undesirable lateral astigmatism in measurable amounts when any part of the lens other than optical center is used. This, in turn, can be aggravated by an Rx with the cylinder correction at odds with the lens fields.



Not so with Younger Seamless Lenses, because these fine lenses are ground on the sound ophthalmic principle that the patient *must* have non-aberrated distance and reading areas for efficient vision. To achieve this, Youngers are ground with only a narrow transition zone between two optically correct powers which can be instantly checked with conventional instruments merely by masking off the transition zone and taking a reading as on any ordinary bifocal!

And if you're concerned about the width of the transition zone, be assured that it is *narrow!* It's true the original Younger Lens had a wide transition zone, but credit fifteen years of constant research and modern technology for reducing this zone to manageable width.

If you haven't inspected a Younger Seamless Lens recently, do so now. You'll be pleasantly surprised and your patients will be exceptionally grateful. Remember: if your patient isn't satisfied, the lenses will be replaced with multifocal blanks of your choice.

**Younger Lenses are available through most independent labs and all American Optical branches . . . in glass or hard resin.**

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## sterile, disposable cautery designed especially for the ophthalmic surgeon

**Optemp offers the ocular surgeon these important advantages...**

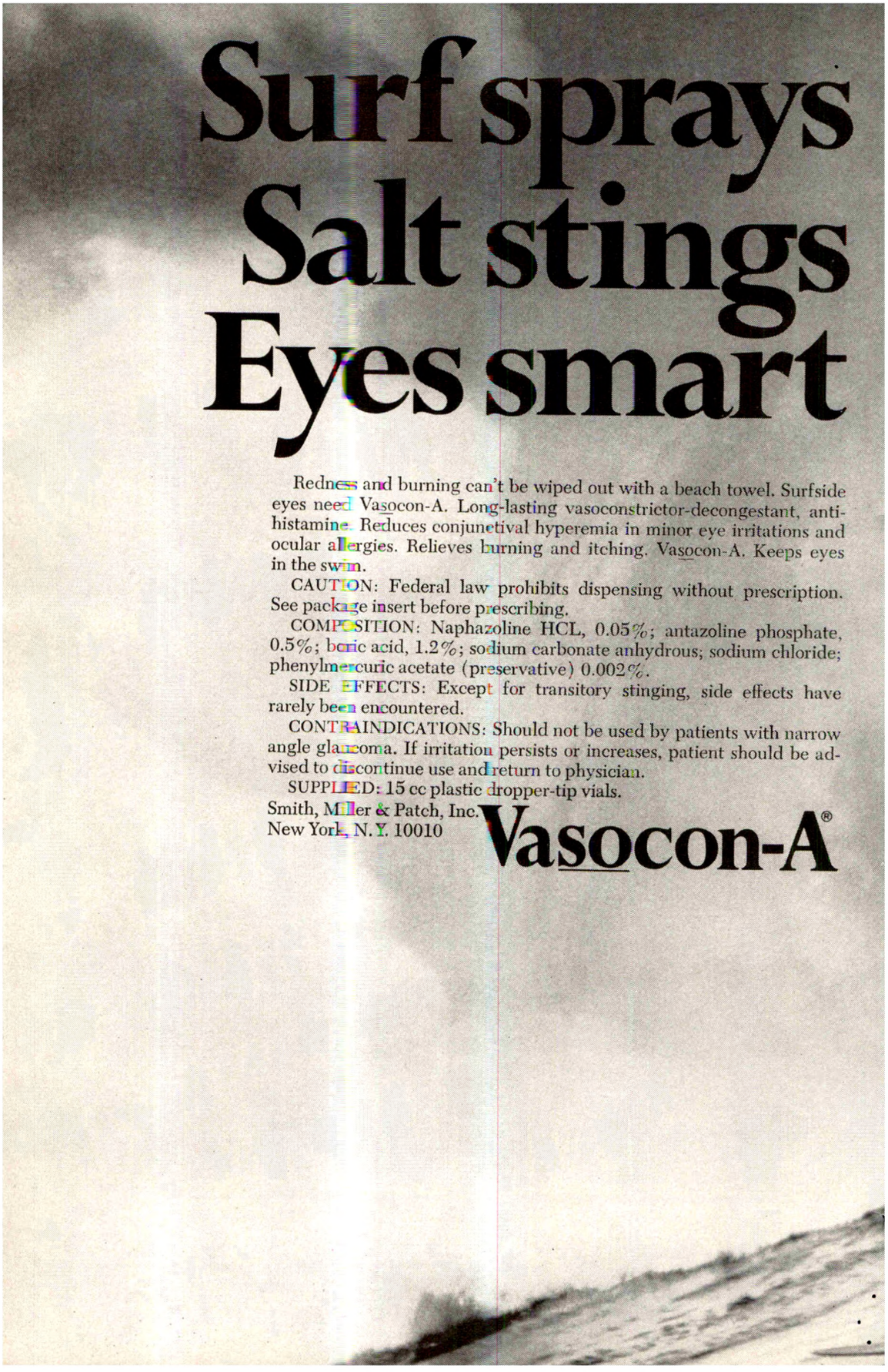
**optimal temperature**
Optemp is only 300°C at the tip...hot enough for instant occlusion of individual capillaries, "cool" enough to minimize damage to surrounding tissues

**excellent visibility**
Optemp, with an elongated operating tip, offers the surgeon an unrestricted field of vision...the instrument, being light weight and well balanced, is easily maneuverable with no cumbersome cords to get in the way.

**sterility, economy**
Optemp is sterile as received, eliminates the possibility of cross-infection... battery powered and inexpensive, it saves on resterilization and reprocessing.

Ask for Optemp at your local hospital and see why it's the dependable ophthalmic cautery that meets your needs in every way.

Surgical Products Division,
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Redness and burning can't be wiped out with a beach towel. Surfside eyes need Vasocon-A. Long-lasting vasoconstrictor-decongestant, antihistamine. Reduces conjunctival hyperemia in minor eye irritations and ocular allergies. Relieves burning and itching. Vasocon-A. Keeps eyes in the swim.

CAUTION: Federal law prohibits dispensing without prescription. See package insert before prescribing.

COMPOSITION: Naphazoline HCL, 0.05%; antazoline phosphate, 0.5%; boric acid, 1.2%; sodium carbonate anhydrous; sodium chloride; phenylmercuric acetate (preservative) 0.002%.

SIDE EFFECTS: Except for transitory stinging, side effects have rarely been encountered.

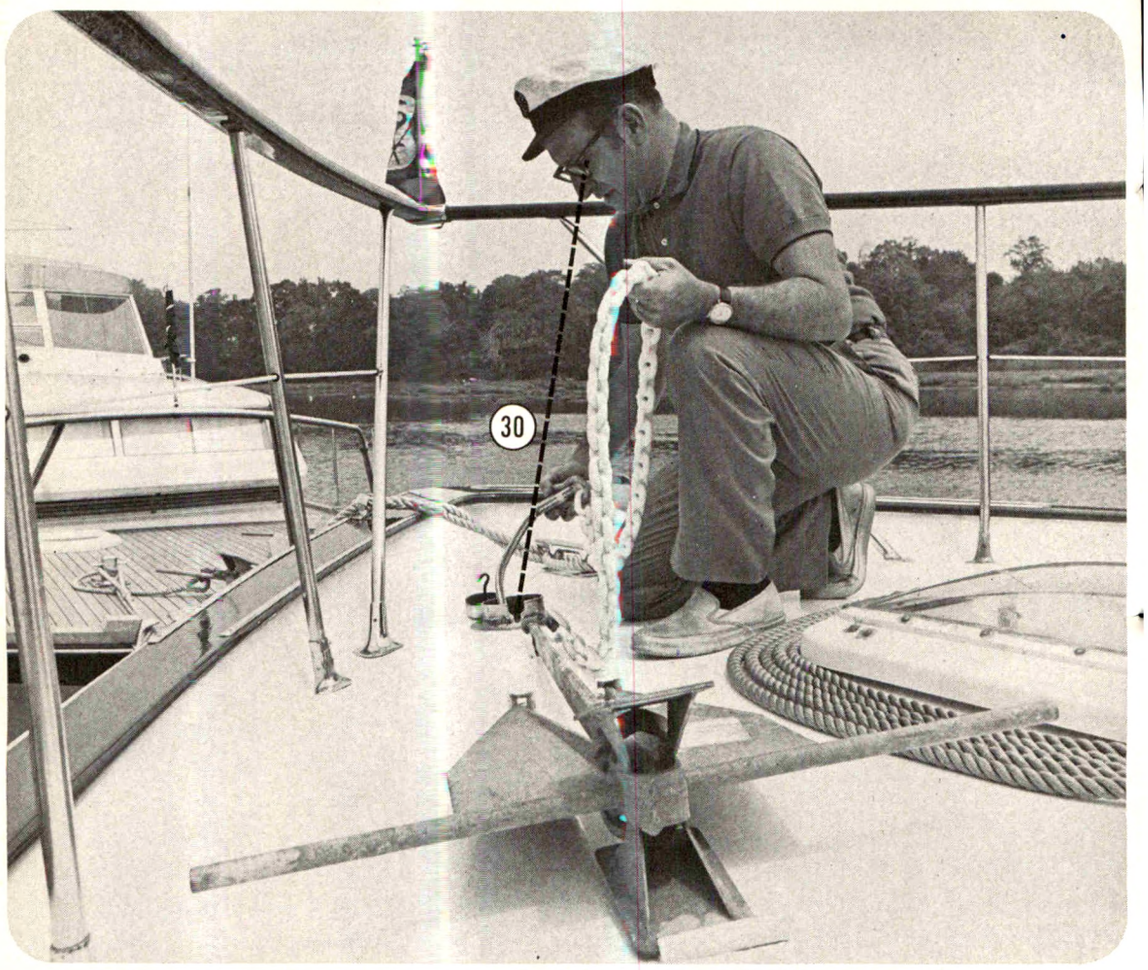
CONTRAINDICATIONS: Should not be used by patients with narrow angle glaucoma. If irritation persists or increases, patient should be advised to discontinue use and return to physician.

SUPPLIED: 15 cc plastic dropper-tip vials.

Smith, Miller & Patch, Inc.
New York, N.Y. 10010

**Vasocon-A®**






*Occupational Vision Studies*
*(From Study #25, Volume II, Guide to Occupational and Other Visual Needs)*

# Boating

(Power Boats)

When "boating" is mentioned as an occupation or an avocation, the first thought that comes to mind is "glare protection", which is a perfectly obvious visual need of the man who spends time on the water.

What is not generally recognized is that the boating enthusiast has an astonishing range of vision needs, from the ability to read the fine print of a chart through the arm's-length requirements of power boat operation to the good distance vision necessary to travel over large expanses of water.

And when you consider that the sailor also may maintain his own machinery, tie fishing flies and need to judge distances accurately, it is perfectly obvious that he has a much wider range of vision needs than appears on the surface.

That's where Vision-Ease comes in, because there is a Vision-Ease multifocal form for any of the boat operator's needs. Ask your lab.

VISION-EASE®

THE VISION-EASE CORPORATION
St. Cloud, Minnesota 56301

***Vision-Ease has a one-quality line . . . the finest.***
***This is what your patient gets when you specify Vision-Ease.***


Surprise!

# Here's a gift from us to you to your patient

When you receive your Obrig/MCLS Auto-Edged* contact lenses, your patient gets an unexpected surprise package. We call it the Obrig Patient Kit and it includes your patient's lenses, plus starter packages of the new contact lens solutions from Milroy Laboratories,** another member of the now famous Milton Roy family. Just one more example of the increasing depth of research and development provided you by Obrig/MCLS.

For additional information and price list on the new Obrig contact lens solution contact:

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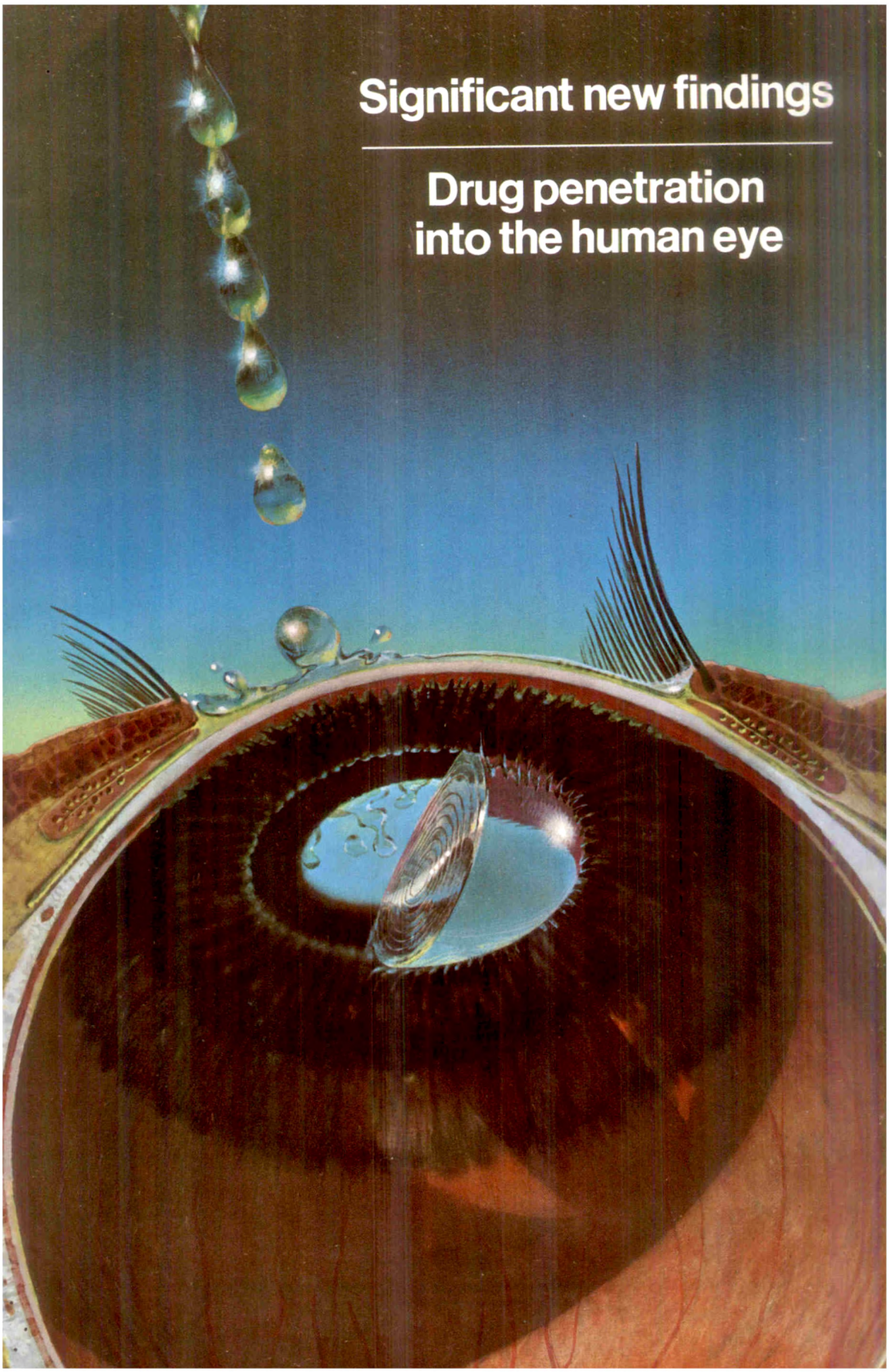
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Significant new findings
Drug penetration
into the human eye

# for the first time independent research relates ocular drug penetration in humans to your choice of ophthalmic vehicles

## Proof of penetration—new fluorophotometry concentration/duration study[1]

Using a slit lamp fluorophotometer, "the effects of ophthalmic vehicles on the intraocular penetration of topical fluorescein in man" were determined. "Quantitative data on ocular penetration of this drug, in man, in vivo, are presented."

### The study

Fluorescein combined with hydroxypropyl methylcellulose 0.5%, polyvinyl alcohol 1.4% and aqueous; each vehicle instilled in the eyes of 20 normal subjects; each subject served as his own control; hourly measurements of attained drug concentration were made quantitatively using a slit lamp fluorophotometer.

### The findings

CORNEA

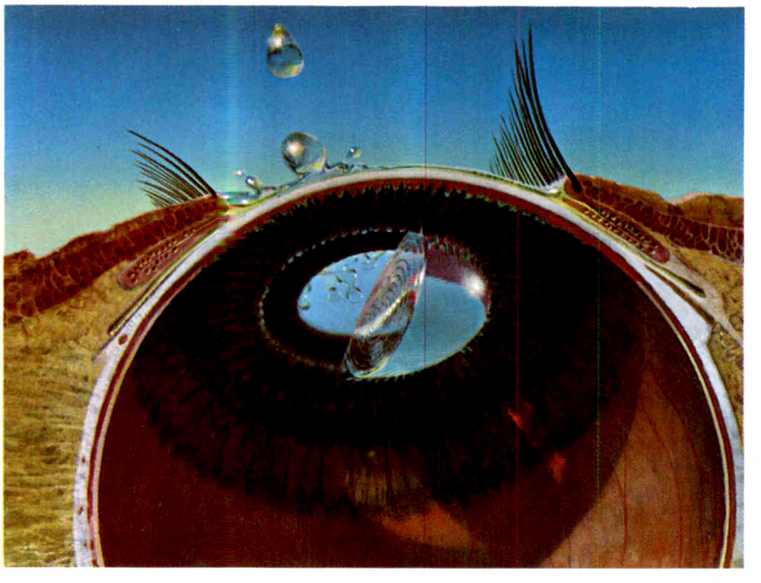
Over a three hour period, hydroxypropyl methylcellulose produced corneal drug levels 85% higher than polyvinyl alcohol and 43% higher than the aqueous vehicles.‡

AQUEOUS HUMOR

Over a three hour period, hydroxypropyl methylcellulose produced aqueous humor drug levels 93% higher than polyvinyl alcohol and 42% higher than the aqueous vehicle.‡‡

### The authentication

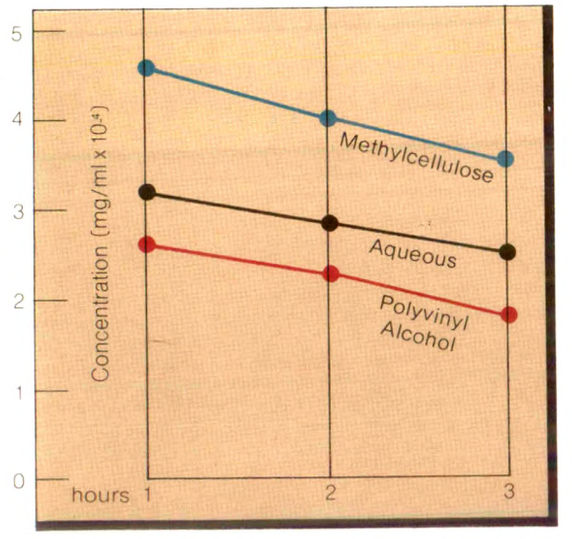
The authors state that their findings may, or may not, be true for drugs other than fluorescein. However, the findings reported above were achieved "consistently and reproducibly"; data were analyzed and tested for significance on a computer.



Isopto® vehicle (hydroxypropyl methylcellulose 0.5%)
produced significantly higher drug penetration and concentration
compared with 1.4% polyvinyl alcohol or aqueous vehicles.

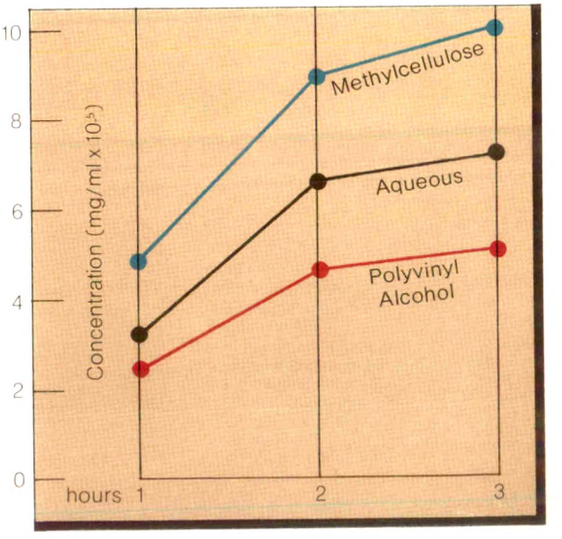
‡Concentration in human cornea

Corneal fluorescein concentration after topical 2% fluorescein in various vehicles.




‡‡Concentration in human aqueous humor

Aqueous humor fluorescein concentration after topical 2% fluorescein in various vehicles.




Adapted from Waltman, S.R. and Patrowicz, T.C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man, Invest. Ophthal. 9:966, 1970.

...therefore, when penetration makes the clinical difference

# when infectious inflammations demand a long-lasting sulfa/steroid

The Isopto® Cetapred vehicle makes for greater concentrations[1] of drug in ocular tissue. Combined with broad, anti-infective range, the high levels of anti-inflammatory action provide rapid and prolonged relief of symptoms—pain/hyperemia/exudation—greater therapeutic efficacy, and maximum patient comfort.

**Cetapred® Ophthalmic Preparations:**

**Description:** *Solution:* Sterile, containing: *Active:* Sodium Sulfacetamide 10%, Prednisolone Acetate 0.25%; *Vehicle:* Hydroxypropyl Methylcellulose 0.5%: *Preservatives:* Thimerosal 0.01%, Sodium Thiosulfate 0.1%; *Inactive:* Sodium Biphosphate, Dried Sodium Phosphate, Hydrochloric Acid (to adjust pH), Purified Water.

**Ointment:** Sterile, containing: *Active:* Sodium Sulfacetamide 10%, Prednisolone Acetate 0.25%; *Preservatives:* Methylparaben 0.05%, Propylparaben 0.01% *Inactive:* White Petrolatum, Anhydrous Liquid Lanolin, Mineral Oil.

**Precautions—Adverse Reactions:** Extended use may cause increased intraocular pressure, which should be checked frequently. Perforation may occur in diseases causing thinning of the cornea. Institute other therapy if favorable response is not obtained within reasonable period. Discontinue if sensitivity occurs.

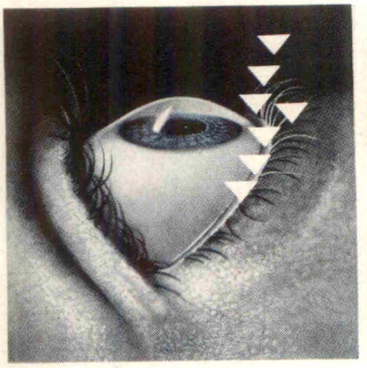
**Contraindications:** tuberculosis, fungal, and most viral lesions of the eye; vaccinia; varicella; acute purulent conjunctivitis, acute purulant blepharitis.

**Supplied:** In 5 cc and 15 cc Drop-Tainer® dispensers; sterile ointment in 1/8 oz. tubes.

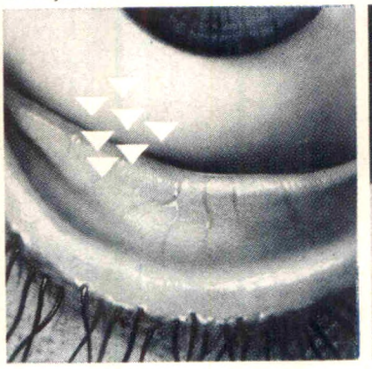
**References: 1.** Waltman, S.R. and Patrowicz, T.C.: Invest. Ophthal. 9:966, 1970.
**2.** Linn, M.L. and Jones, L.T.: Amer. J. Ophthal. 65:76, 1968.

# long-lasting activity at these demand sites:

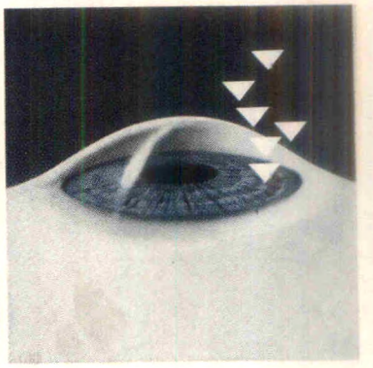
Lid



Conjunctiva



Cornea



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extended surface coverage (over *cornea, conjunctiva, lids*)

extended contact time—resists drug washout[2]

extended activity and corneal penetration

Alcon

# ISOPTO® CETAPRED

sodium sulfacetamide 10%; prednisolone acetate* 0.25%;
vehicle: hydroxypropyl methylcellulose 0.5%

Penetrates into cornea and conjunctiva...
and stays there longer

and for uninterrupted therapy...at night, add
*sterile* Cetapred® Ointment

*Licensed under U.S. Patent 3,134,718

# NEW DEVELOPMENTS . . .

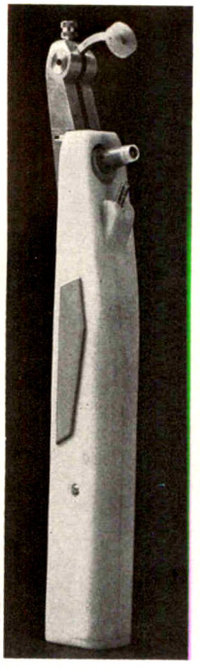


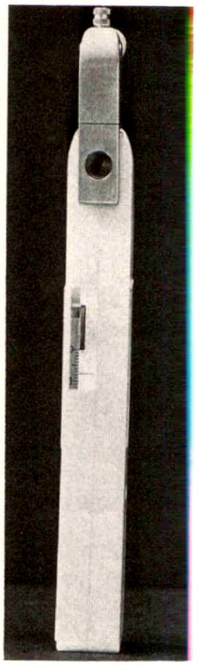
## ORA SERRATA ATTACHMENT TO THE GOLDMANN 3 MIRROR LENS

The periphery of the fundus near the ora serrata and the ciliary body cannot be examined under normal conditions with the 3-mirror lens alone. The ora serrata attachment along with the 3-mirror lens allows the observation of these most peripheral parts in its entire circumference.

The attachment is shaped like the 3-mirror lens. Half a steel-ball is fixed to the scleral part of the attachment which presses on the sclera above the ora serrata so that the fundus at its periphery near the ora serrata can be seen in the gonio mirror of the 3-mirror lens. The ora attachment can be used either with the 3-mirror lens in a locked or moveable position.

# THE PERKINS HAND HELD APPLANATION TONOMETER

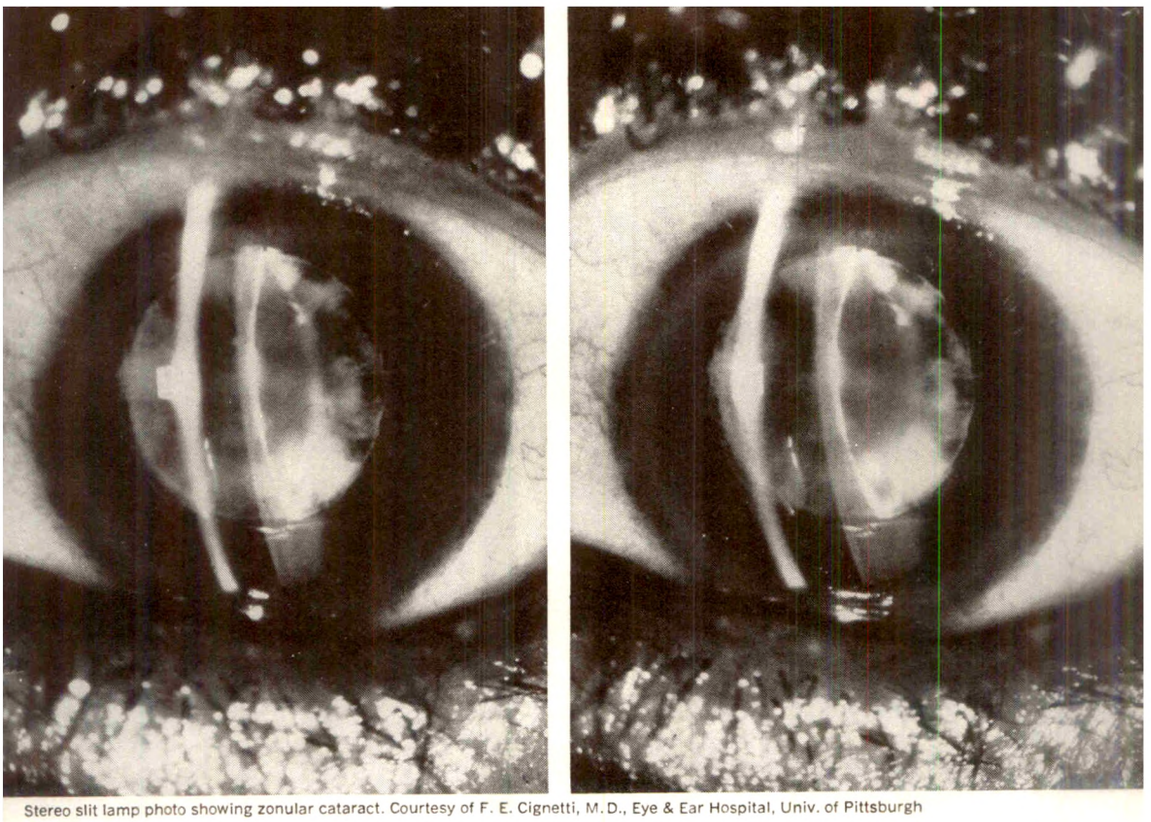




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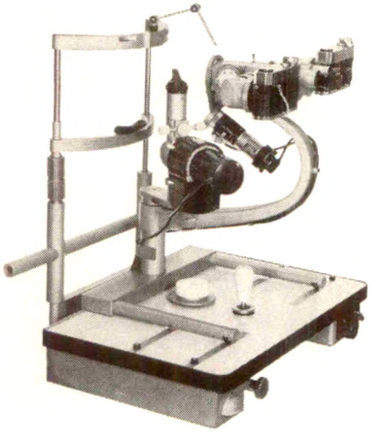
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Stereo slit lamp photo showing zonular cataract. Courtesy of F. E. Cignetti, M.D., Eye & Ear Hospital, Univ. of Pittsburgh

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And, second, you can do it stereoscopically. Stereo slit lamp photos are as superior to conventional photos as 3-dimensional biomicroscopy is to examination with a monocular microscope. And since observation is uninterrupted during photography, you are assured of recording exactly what you see. A wide variety of attachments provides unmatched photographic versatility. You can, of course, use the Photo Slit Lamp, too, for regular biomicroscopy.

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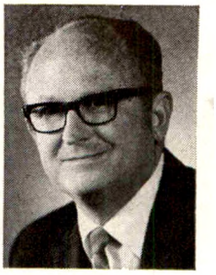
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Recognizing this need, we have formed UNION OPTICS CORPORATION, comprising a select group of established laboratories under the leadership of respected contact lens authorities. This organization is now the second largest contact lens manufacturing entity in the U.S.A. We expect it to play a major part in research, development and improvement of contact lenses in the future.

If you are not yet acquainted with our laboratories, we invite you to get in touch with the one nearest you.

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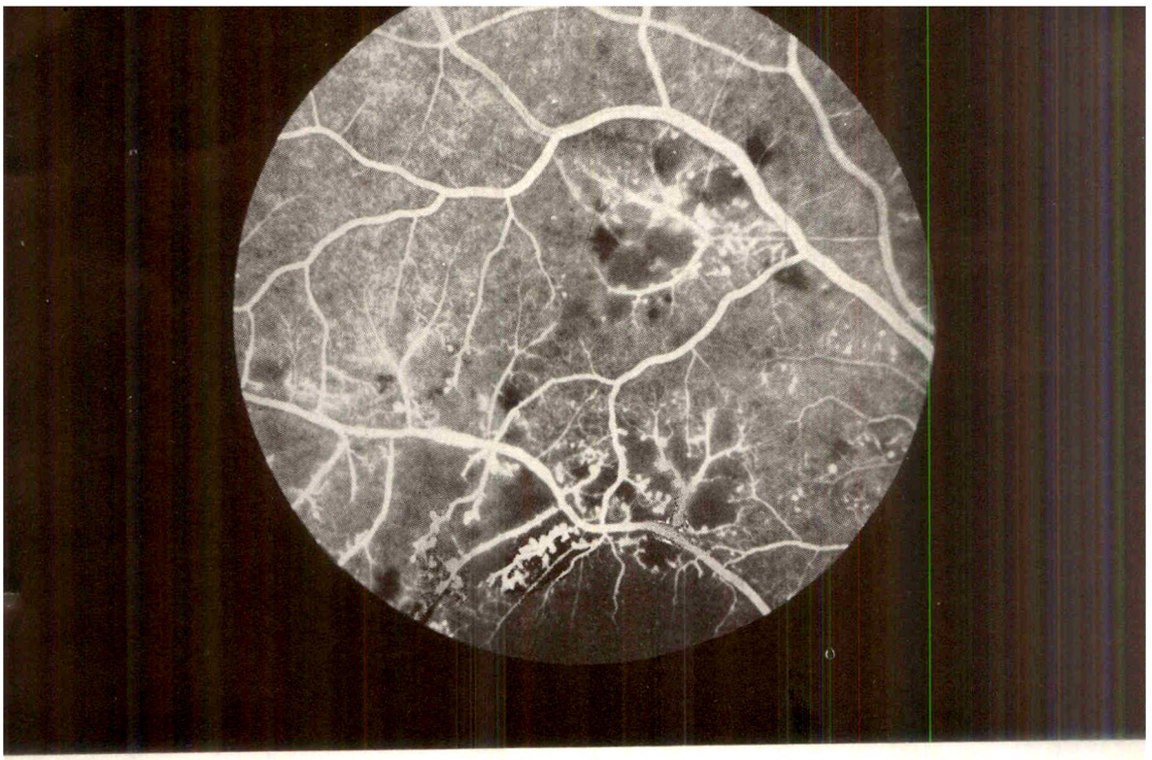
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# Look what fluorescein fundus photography can tell you.

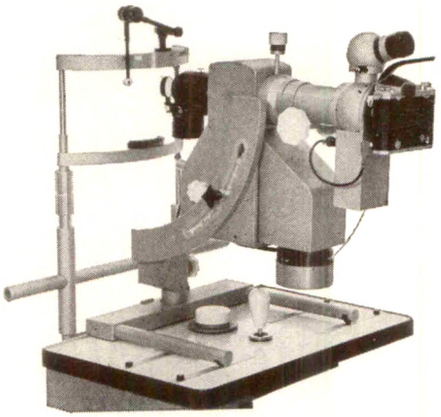
This fluorescein angiogram of a diabetic retinopathy, revealing a gross vasculopathy in micro and macro vessels, is only one example of the results that can be easily obtained with the new Zeiss Fundus Flash II. Of the many features of this unique instrument, four are particularly worth citing here:

(1) The light source, adjustable for low, medium or high intensity, with low heat, fast recycling, short warm-up (0.5 sec.) and long flash tube life.

(2) The built-in digital data timing system which indicates automatically the time lapse between photographs.

(3) The control system which allows preselection of frame sequences from 1 to 4 frames/sec., time exposures, and automatic shutoff of film transport after a selected number of frames.

(4) The exclusive Allen Stereo Separator for taking stereo photographs automatically with no equipment adjustment.



For complete details on the many other features of this easy-to-use instrument, write Carl Zeiss, Inc., 444 5th Avenue, New York, N.Y. 10018.

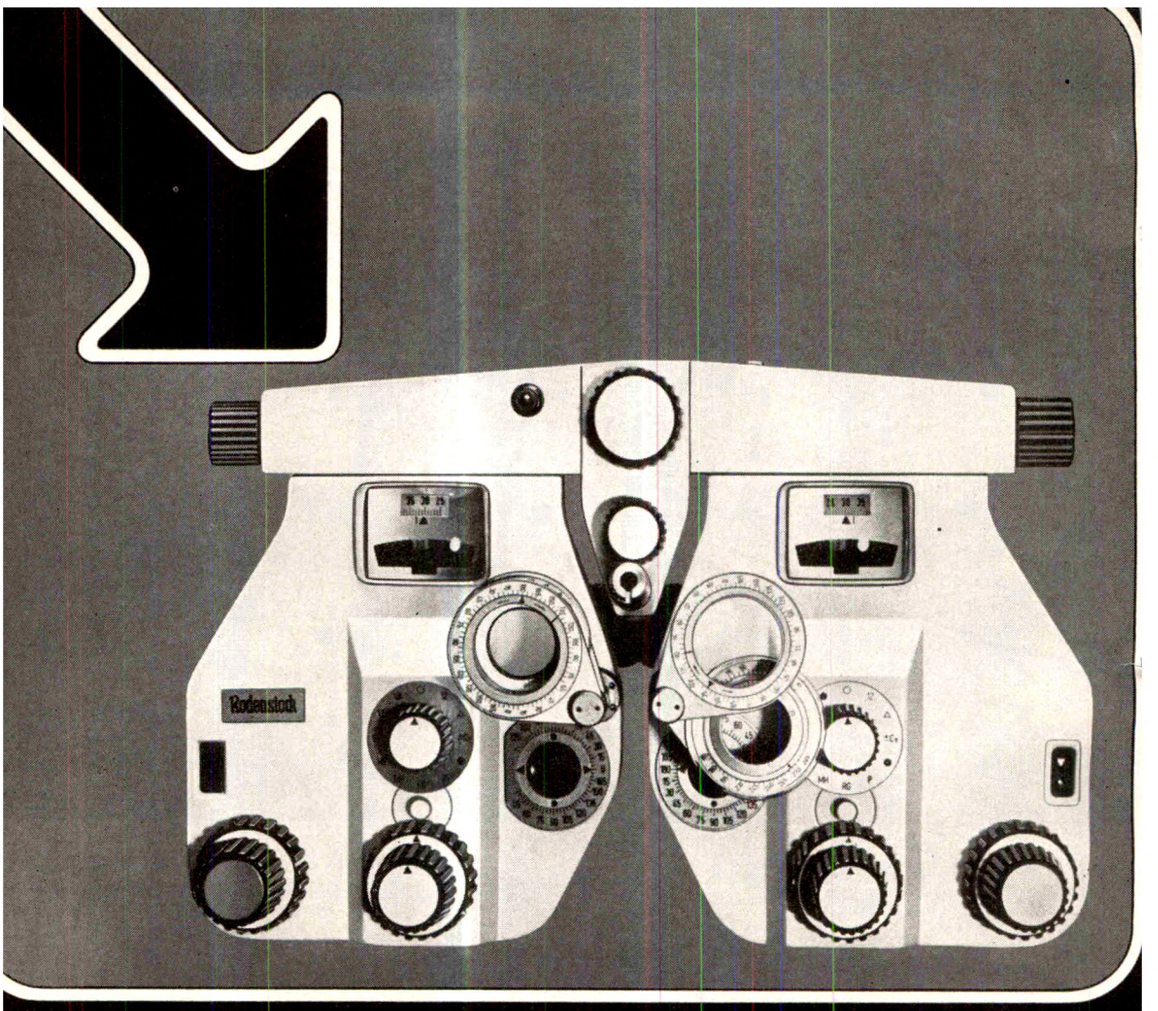
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# horopter

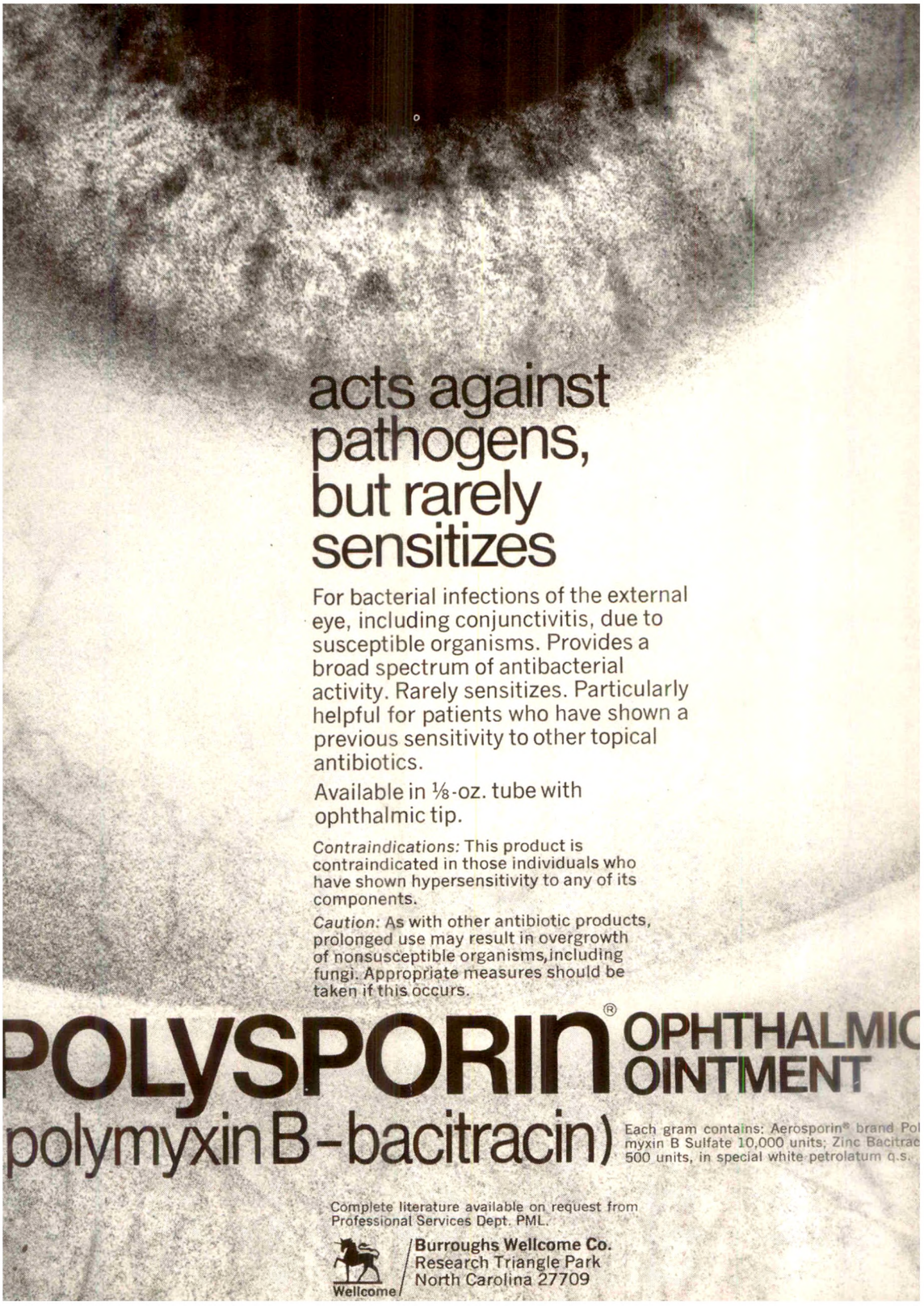
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Available in ⅛-oz. tube with ophthalmic tip.

*Contraindications:* This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

*Caution:* As with other antibiotic products, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

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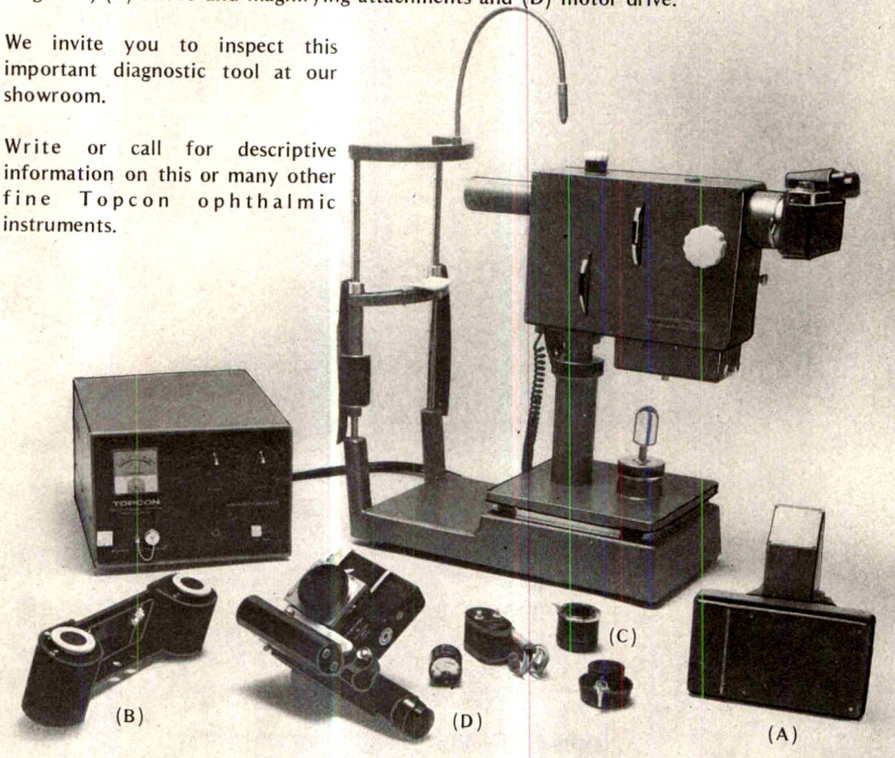
RETINAL CAMERA Model TRC-F I

The TOPCON Retinal Camera, Model TRC-F, is an accurate, well designed instrument ideal for obtaining distinct 35mm color and black & white photographs of the anterior ocular structures and fundus. Direct observation is possible during fluorescein angiography at two frames per second with a working distance of approximately 75mm from the cornea. The patient's name and frame sequence are recorded on the film.

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# LAST YEAR WE TOLD YOU ABOUT THE "PRESSURE-SPARING" EFFECT OF HMS...

(medrysone)



# ...APPARENTLY YOU WANT TO KNOW MORE.

# SO TAKE THIS NEW LOOK AT HMS.

Drawing on nearly seven years of extensive clinical research experience, let's consider those questions you have asked most frequently.

### "Is HMS too mild to benefit my patients with inflammatory conditions?"

In the past five years, numerous independent studies on HMS (medrysone) have been published including those by Becker, and Thygeson.[1-4] Virtually all have reached the same conclusions: HMS is an effective treatment for superficial ocular inflammations.

Additionally, in a recent survey, 76% of the ophthalmologists interviewed who had tried HMS, found it effective when used for the recommended conditions.[5]

### "What therapeutic possibilities are now open to me, with HMS, that were not available with other mild steroids?"

First, over 30% of the population is likely to respond to steroids with an intermediate to high increase in intraocular pressure; steroid use with these patients must therefore be selective and cautious.[6] With HMS, most of these patients now can safely receive long-term steroid treatment.

Secondly, there are those glaucoma patients who must be treated specifically with epinephrine but are nevertheless sensitive to this drug. With HMS as concomitant therapy, Becker and Kolker reported that there was "sufficient improvement in glaucoma control so as to avoid surgery" by allowing continuation of epinephrine therapy.[7]

### "I haven't seen a rise in IOP with mild steroids. Isn't the real concern with the more potent steroids?"

There is ample evidence that .1% dexamethasone produces significant increases in IOP[1,4,8], and even .12% prednisolone, the mildest of the commercially available ophthalmic steroids, has the potential to increase IOP. Conversely, Doctors Becker and Kolker found in their investigational study that "medrysone (HMS) can be administered to patients four times a day for periods of several months with essentially no elevation of intraocular pressure even in individuals highly susceptible to such elevation."[7]

### "Can I treat uveitis and iritis with HMS?"

It is *not* indicated for these conditions. Its merits should only be judged in those conditions where indicated: allergic and vernal conjunctivitis, episcleritis, and epinephrine sensitivity.

### "Is HMS uncomfortable for the patient to use?"

Results of a recent patient study showed that 96% of those tested found HMS completely comfortable in the eye.[9] Though early batches of the product did cause some minor irritation to the eyes of a few patients, this has not been a recurring problem.

HMS® (medrysone)
LIQUIFILM® OPHTHALMIC SUSPENSION

ALLERGAN

Please see next page for Prescribing Information.

Prescribing Information for

# HMS®(medrysone)

LIQUIFILM® OPHTHALMIC SUSPENSION

DESCRIPTION: Contains:
medrysone.....1.0%
Liquifilm® (polyvinyl alcohol).....1.4%
with: benzalkonium chloride, disodium edetate, sodium chloride, potassium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, methylcellulose, purified water, and sodium hydroxide or hydrochloric acid if needed to adjust pH. HMS (medrysone) is related structurally more to progesterone than to other available corticosteroids.

INDICATIONS: HMS (medrysone) is effective in the treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis and epinephrine sensitivity. HMS (medrysone) is not indicated in iritis or uveitis as its therapeutic effectiveness has not been demonstrated.

CONTRAINDICATIONS:
HMS (medrysone) is contraindicated in the following conditions:

1. Acute untreated purulent ocular infections.
2. Acute herpes simplex (dendritic) keratitis.
3. Viral diseases of the conjunctiva and cornea.
4. Ocular tuberculosis.
5. Fungal diseases of the eye.
6. Hypersensitivity to any of the components of the drug.

WARNINGS:

1. Infectious diseases of the eye may be masked, enhanced or activated by steroids.
2. Corneal or scleral perforation occasionally has been reported with prolonged use of topical steroids. In high dosage they have been associated with corneal thinning.
3. Prolonged use of topical steroids may increase intraocular pressure although data from 2 uncontrolled studies[4,7] indicate that in patients with increased intraocular pressure and in those susceptible to a rise in intraocular pressure upon application of topical steroids, there is less effect on pressure with HMS than with dexamethasone or betamethasone.
4. Prolonged use of topical corticosteroids may rarely be associated with development of posterior subcapsular cataracts.
5. Systemic absorption and systemic side effects may result with the use of topical steroids.

PRECAUTIONS:

1. HMS (medrysone) is not recommended for use in iritis and uveitis as its therapeutic effectiveness has not been demonstrated in these conditions.
2. With prolonged use of HMS (medrysone) the intraocular pressure and lens should be examined periodically.
3. In persistent corneal ulceration where a steroid has been used, or is in use, fungal infection should be suspected.
4. The use of topical steroids in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother.

ADVERSE REACTIONS: Occasional transient stinging and burning may occur on instillation.

DOSAGE AND ADMINISTRATION: One drop instilled in the conjunctival sac up to every four hours.

SUPPLY:
As a 5 cc. sterile suspension in plastic dropper bottles on prescription only.

NOTE: Bottles filled to one-half capacity for proper drop control. Do not freeze.

REFERENCES:


1. Drance, S.M. and Scott, S.: A Comparison of Action of Dexamethasone and Medrysone on Human Intraocular Pressure. Canad. J. Ophth., 3:159, 1968.
2. Bedrossian, R. H., and Eriksen, S. P.: The Treatment of Ocular Inflammation with Medrysone, Arch. Ophth., 81:184, Feb., 1969.
3. Dorsch, W., and Thygeson, P.: The Clinical Efficacy of Medrysone, A New Ophthalmic Steroid, Amer. J. Ophth., 65:74, Jan. 1968.
4. Spaeth, G. L.: An Anti-Inflammatory Steroid Without Apparent Effect on Intra-Ocular Pressure, Arch. Ophth., 75:783, 1966.
5. Data on file, Allergan Marketing Department.
6. Armaly, M. F.: Factors Affecting the Dose Response Relationship in Steroid-Induced Ocular Hypertension, Chapter VII, Ocular Anti-Inflammatory Therapy, Ed. by H. E. Kaufman, Charles C. Thomas, Springfield, Ill., 1970, pp. 88-97.
7. Becker, B., and Kolker, A. E.: Intraocular Pressure Response to Topical Corticosteroids, Chapter 9, Ocular Therapy, Complications and Management, Ed. by I. H. Leopold, The C. V. Mosby Co., St. Louis, 1967, pp. 79-83.
8. Nelson, E. L., Ophthalmic Steroids, Chapter XVII, Ocular Anti-Inflammatory Therapy, Ed. by H. E. Kaufman, Charles C. Thomas, Springfield, Ill., 1970, pp. 217-233.
9. Data on file, Allergan Research Department.


ALLERGAN Irvine, California/Montreal, Canada


**FELLOWSHIPS AVAILABLE**

•

The Heed Ophthalmic Foundation provides fellowships for advanced study or research in ophthalmology. Applicants must be graduates of medical schools accredited by the American Medical Association and citizens of the United States. Deadline for submission of applications: December 31 for a fellowship starting the following July. Please direct all inquiries and requests for application forms to:

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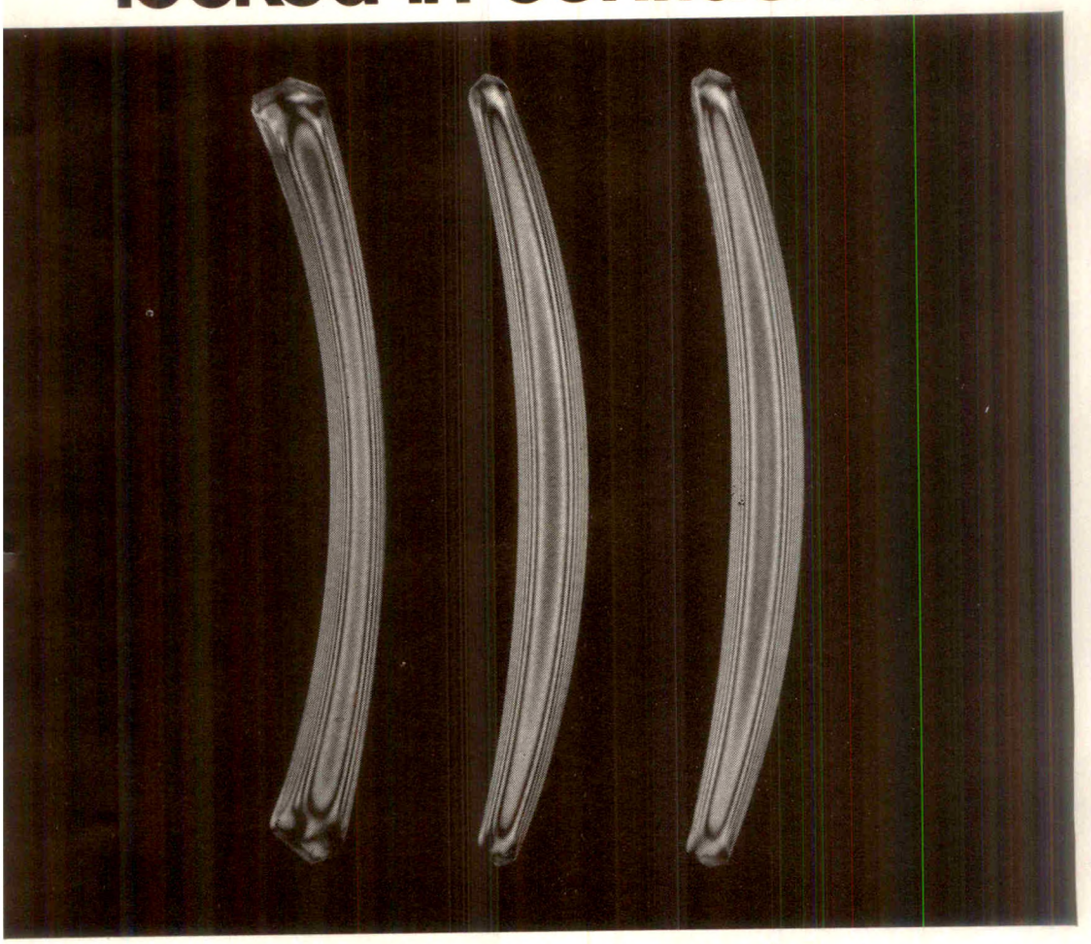
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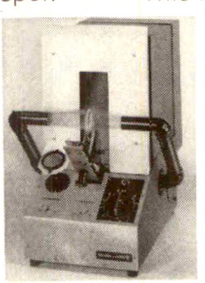
# locked-in confidence



## A Closed Envelope of Compression Means Full Impact Resistance from Center to Bevel Crown

Legislation requiring impact-resistant lenses in all prescriptions is on the books in several states. A federal regulation requiring them is being considered. And with these acts comes the unsettling question of responsibility and liability for the protective lenses you dispense.

This unique and unretouched photograph shows in cross section three lenses heat-treated in a B&L Compact Heat-Treating Unit. Polarized light reveals the evenly balanced, compression-expansion stress structure that imparts so much extra strength. The continuous dark line marks the boundary between tension and compression layers. You can see that the compression layer is closed and uniformly thick; there are no openings for tension "leaks" or soft spots to give way under a tension shift.

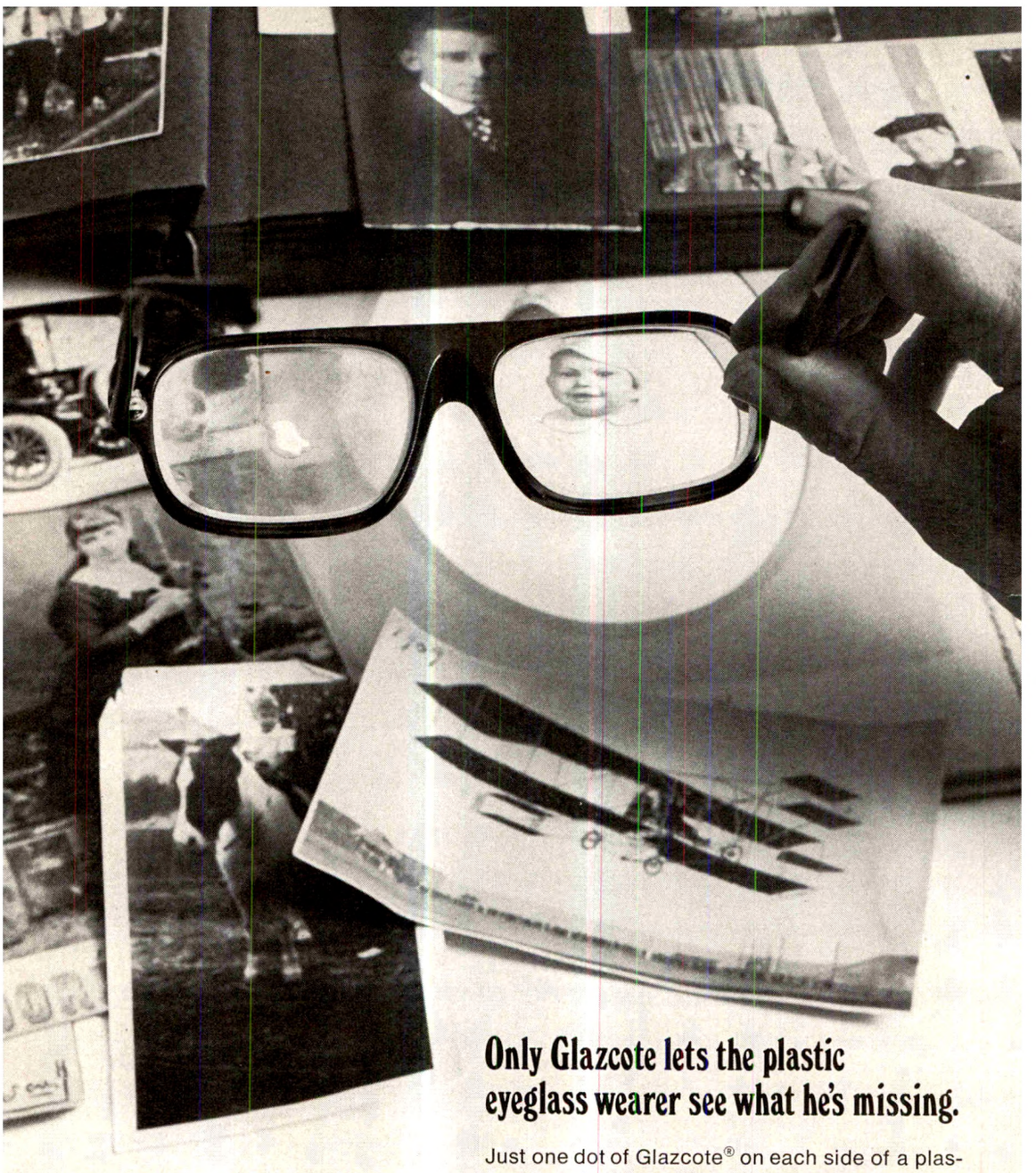


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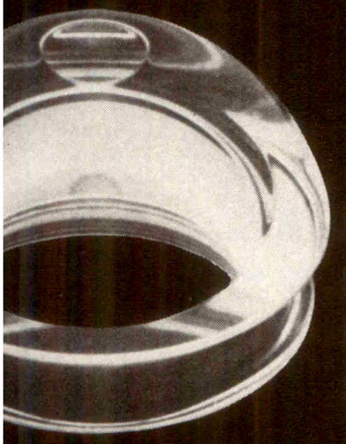


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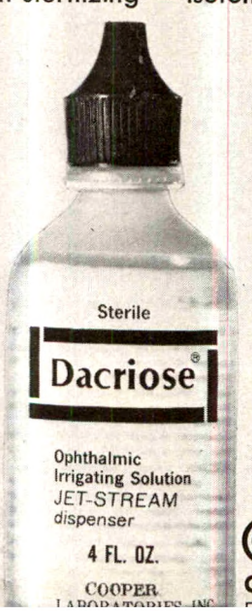
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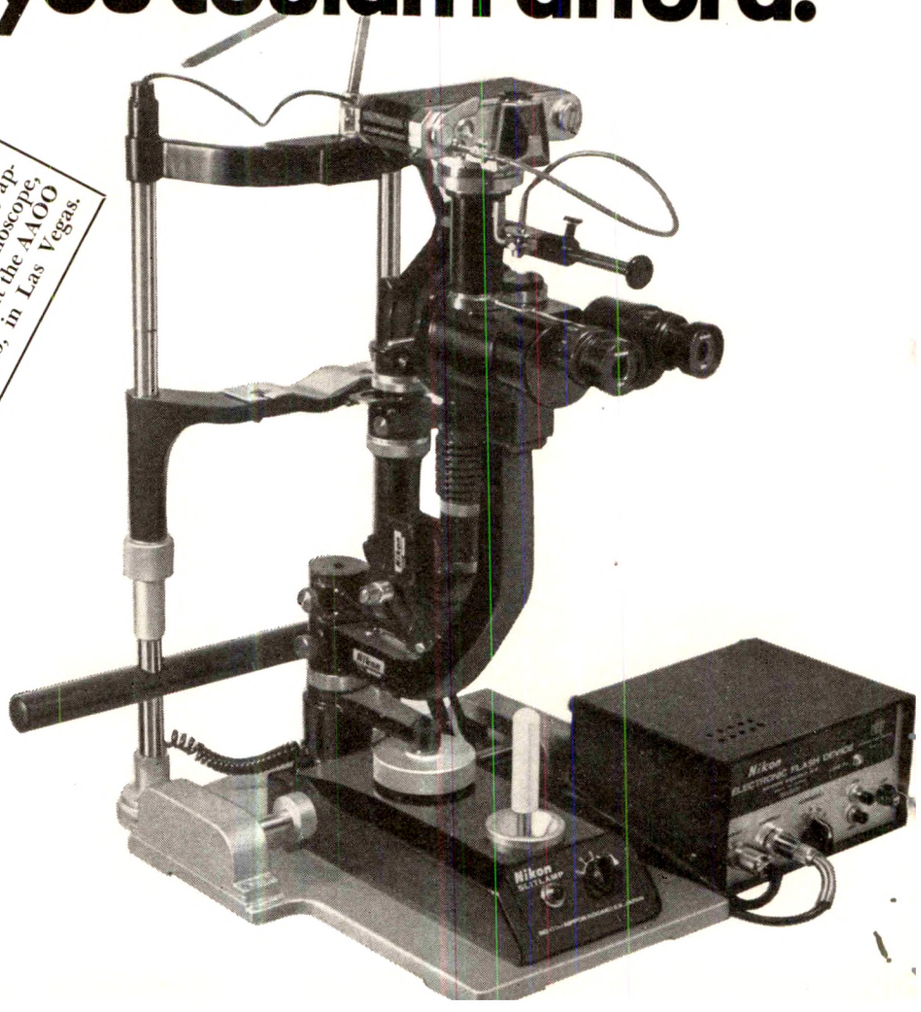
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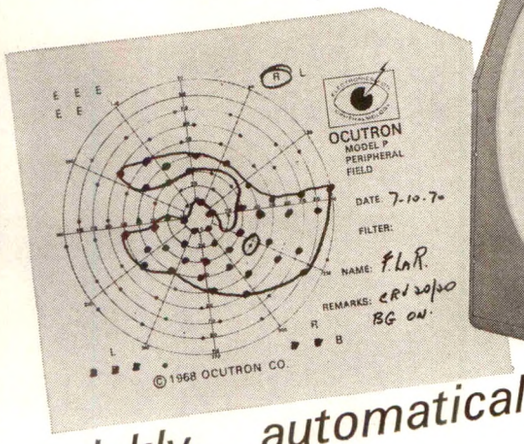
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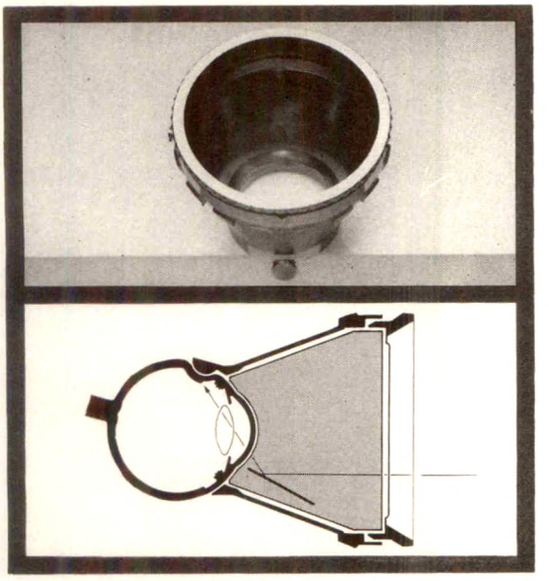
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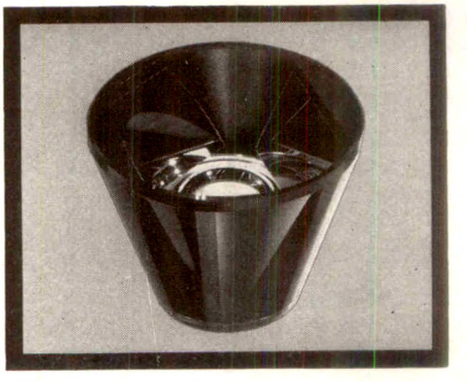
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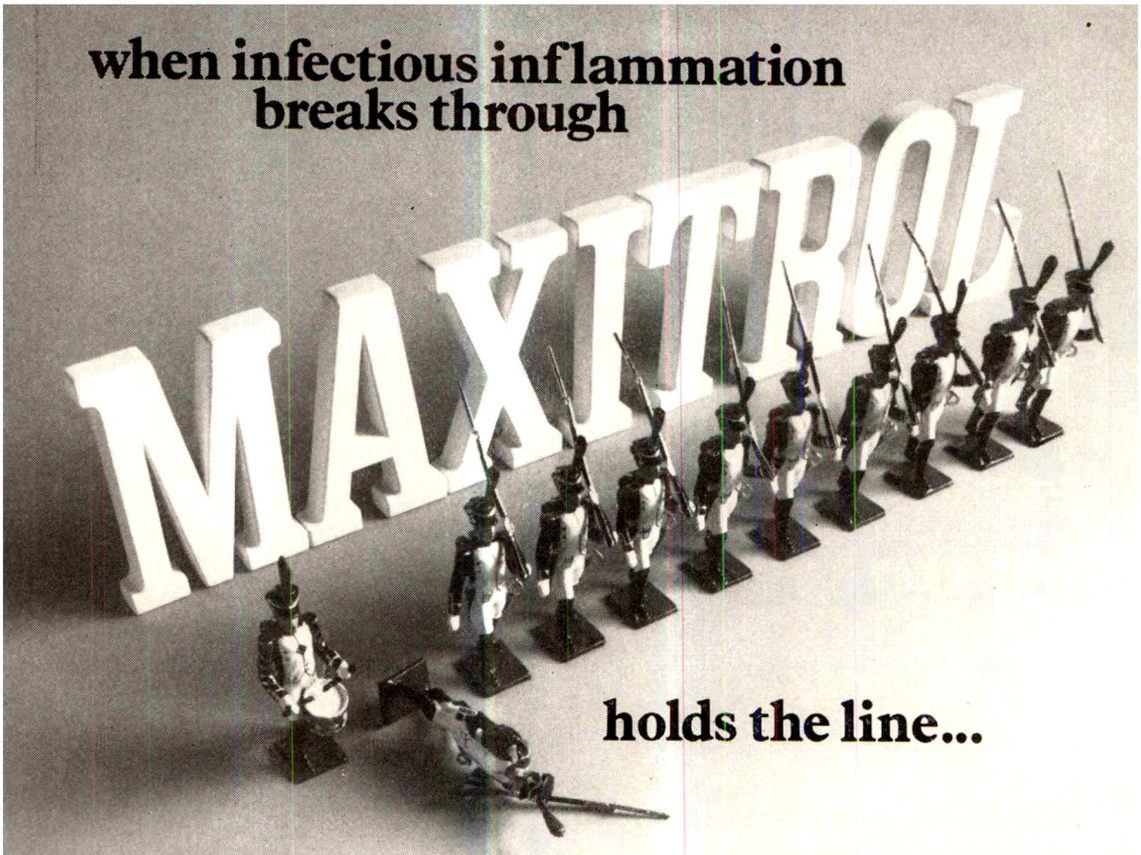
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References: 1. Nelson, E. L.: "Ophthalmic Steroids," in Kaufman, H. E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970. 2. Waltman, S. F. and Patrowicz, T. C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

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# PHOTOCOAGULATION IN DIABETIC RETINOPATHY

A. E. KRILL, M.D., D. B. ARCHER, F.R.C.S., F. W. NEWELL, M.D. AND M. I. CHISHTI, M.D.

*Chicago, Illinois*

In 1966 we initiated a controlled study of the treatment of diabetic retinopathy by means of retinal photocoagulation in which we treated one eye and followed the natural course of the disease in the untreated eye. Fifty-six of these patients have been followed for one year or more after treatment and their cases are considered to be of value in assessing the effects of photocoagulation.

## MATERIALS AND METHODS

Pertinent parameters of these patients' diabetic histories, vision, and ocular findings are recorded in Table 1. These include age at which diabetes was diagnosed, age at which retinopathy was first observed, age at treatment, visual acuity before photocoagulation and at final follow-up visit, duration of follow-up, and classification data. Thirty-three patients were followed for 12 to 23 months, 14 for 24 to 35 months, and nine patients for 36 to 48 months.

Twelve patients had vision of 20/60 or better in each eye. Twenty-four patients had vision of 20/60 or better in one eye and 20/100 or worse in the other eye. Sixteen patients had vision of 20/100 or worse in both eyes. The four remaining patients did not fit readily into any of the groups (two had 20/80–20/200 vision; the other two had 20/80–20/30 vision). Visual acuities for all patients before and after treatment are shown in the table.

*Ocular evaluation*—In addition to routine examination, this included: perimetry with the Goldmann perimeter where possible; color photography with the Zeiss fundus camera; fluorescein angiography[1] when the media were sufficiently clear; drawings of fundi which could not be photographed or which had significant pathology in the peripheral fundus. Each patient's eyegrounds were assessed according to a classification developed at a symposium on the treatment of diabetic retinopathy held in Warrenton, Virginia, in 1968. This classification, which is described in detail elsewhere,[2] is now referred to as the Airlie classification (Fig. 1).

In the great majority of cases, photographs were used for evaluation. However, 23 eyes could not be classified because of dense vitreous hemorrhage, massive far-advanced proliferative retinopathy, or a combination of both.

Proliferative retinopathy was present in both eyes of 41 patients and in one eye of seven patients. Eight patients had nonproliferative retinopathy in both eyes. We considered the degree of elevation in the designation of proliferative retinopathy as early, moderate, or advanced. Proliferative retinopathy (PR) within one-fourth disk diameter of surface of attached retina was considered to be early; PR extending anterior to the retina's normal position by one-fourth to two disk diameters was considered to be

From the Eye Research Laboratories, University of Chicago. This study was supported in part by Public Health Service Grants EY-0523-09, EY-0277-05, and RR-55.

Reprint requests to Alex E. Krill, M.D., Eye Research Laboratories, University of Chicago, 950 East 59th Street, Chicago, Illinois 60637.

TABLE 1

CLASSIFICATION*

| Case No., Age, and Sex | Age at Onset of Diabetes | Age at Onset of Visual Disturbance | Nonproliferative | | | | Proliferative | | | | Preretinal | | | | Vitreous Hemorrhage | | | | Acuities | | | | Follow-up in Months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | UE† | | TE† | | UE | | TE | | UE | | TE | | UE | | TE | | UE | | TE | | |
| | | | F‡ | L‡ | F | L | F | L | F | L | F | L | F | L | F | L | F | L | F | L | F | L | |
| 1. 50—M | 29 | 47 | 1 | 1 | 1 | U† | 0 | 0 | 4 | U | 0 | 0 | 3 | U | 0 | 0 | 4.5 | U | 20/20 | 20/20 | 20/200 | 10/200 | 24 |
| 2. 57—F | 33 | 56 | 6 | 6 | 5 | 2 | 8 | 8 | 1 | 0 | 0 | 0 | 0 | 1 | 9 | 0 | 3 | 0 | 20/300 | HM | 10/300 | 20/200 | 12 |
| 3. 61—F | 37 | 58 | U | U | U | 0 | U | U | U | 0 | U | U | U | 0 | U | U | U | 0 | CF | NLP | CF | HM | 40 |
| 4. 56—F | 46 | 53 | U | U | 2 | 2 | U | U | 2 | 4 | U | U | 0 | 0 | U | U | 0 | 0 | LP | ENC | 20/30 | 20/30 | 26 |
| 5. 73—F | 40 | 70 | 2.5 | 3.5 | 6.5 | 4.5 | 0 | 3 | 4 | 3 | 0 | 0 | 2 | 0 | 0 | 0 | 4.5 | 0 | CF | 20/200 | 20/200 | 20/200 | 30 |
| 6. 61—F | 48 | 59 | 6.5 | 6.5 | 6.5 | 6 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 20/200 | 5/200 | 20/80 | 5/200 | 12 |
| 7. 48—F | 32 | 45 | U | U | 2 | 2.5 | U | U | 4 | 3 | U | 6 | 1 | 0 | 9 | 9 | 0 | 0 | HM | HM | 20/40 | 20/25 | 33 |
| 8. 52—M | 47 | 50 | 5.5 | 5.5 | 7 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20/60 | 20/40 | 20/100 | 20/40 | 12 |
| 9. 27—F | 16 | 23 | 5 | 2.5 | 1 | 0 | 8 | 8 | 6 | 2 | 6 | 0 | 6 | 0 | 4.5 | 0 | 4.5 | 0 | 20/300 | CF | 5/200 | 10/200 | 13 |
| 10. 56—M | 29 | 46 | 4.5 | 4.5 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20/25 | 20/25 | 20/20 | 20/25 | 12 |
| 11. 64—F | 59 | 62 | 2 | 2 | 3.5 | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4.5 | 0 | 20/30 | 20/25 | 20/60 | 20/40 | 12 |
| 12. 66—M | 63 | 64 | 5.5 | 8 | 7 | 1.5 | 0 | 4 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 20/60 | 20/60 | 20/300 | 20/80 | 15 |
| 13. 60—M | 33 | 57 | U | U | 3.5 | 1.5 | U | U | 4 | 4 | U | U | 0 | 5 | 9 | U | 4.5 | 6.5 | CF | LP | 20/60 | CF | 30 |
| 14. 51—M | 32 | 49 | U | U | 5.5 | 2.5 | U | U | 4 | 0 | U | U | 0 | 0 | U | U | 4.5 | 0 | 20/100 | CF | 20/60 | 20/40 | 20 |
| 15. 58—F | 30 | 50 | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | 20/300 | CF | HM | ENC | 26 |
| 16. 18—F | 3 | 17 | 7.5 | 3.5 | 7.5 | 2 | 8 | 6 | 8 | 4 | 3 | 0 | 6 | 0 | 0 | 4.5 | 4.5 | 0 | 10/300 | 20/60 | 20/60 | 20/40 | 13 |
| 17. 40—M | 21 | 40 | 2 | U | 3.5 | 1.5 | 2 | U | 3 | 0 | 0 | U | 2 | 1 | 0 | 9 | 4.5 | 0 | 20/60 | 20/70 | 20/60 | 20/25 | 12 |
| 18. 47—F | 37 | 45 | 4.5 | 5 | 5 | 0.5 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20/60 | 20/80 | 20/200 | 20/80 | 23 |
| 19. 75—F | 58 | 70 | 3.5 | U | 4.5 | 2.5 | 8 | U | 2 | 6 | 0 | U | 0 | 1 | 9 | U | 0 | 0 | LP | LP | 20/200 | 20/200 | 16 |
| 20. 34—F | 17 | 26 | 4 | U | 3.5 | 2.5 | 6 | U | 4 | 0 | 5 | 6 | 0 | 0 | 8 | 9 | 0 | 0 | 20/200 | 20/60 | 20/25 | 20/20 | 12 |
| 21. 59—M | 56 | 56 | U | U | 7 | U | U | U | 4 | U | U | U | U | U | U | U | 4.5 | U | HM | CF | 15/300 | LP | 21 |
| 22. 59—F | 39 | 56 | 5 | U | 5.5 | 3 | 2 | U | 4 | 6 | 0 | 6 | 1 | 0 | 0 | 9 | 0 | 0 | 20/300 | HM | 20/60 | 20/60 | 48 |
| 23. 29—F | 8 | 28 | 3.5 | 4 | 3 | 2.5 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 4.5 | 0 | 20/80 | 20/30 | 20/20 | 20/30 | 12 |
| 24. 65—M | 49 | 63 | 6 | 4 | 4.5 | 3.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20/200 | 20/100 | 20/80 | 20/80 | 14 |
| 25. 30—M | 13 | 27 | U | U | 4 | U | U | U | 8 | U | U | U | 3 | U | 9 | U | 9 | U | LP | NLP | CF | CF | 24 |
| 26. 60—M | 44 | 54 | U | U | 3.5 | 0 | U | U | 4 | 0 | U | U | 0 | 0 | U | U | 0 | 4.5 | LP | NLP | 20/30 | 20/20 | 42 |
| 27. 47—F | 44 | 46 | 3 | 4.5 | 4.5 | 5 | 4 | 5 | 5 | 8 | 6 | 0 | 0 | 0 | 9 | 4.5 | 4.5 | 4.5 | 10/200 | 20/30 | 20/40 | CF | 15 |
| 28. 65—F | 56 | 62 | U | U | 8 | 1.5 | U | U | 6 | 1 | U | U | 0 | 0 | U | U | 4.5 | 0 | 20/200 | NLP | 20/200 | 20/60 | 33 |
| 29. 61—F | 50 | 59 | U | U | 5.5 | 5 | U | U | 7 | 8 | U | U | 1 | 5 | U | U | 4.5 | 4.5 | HM | HM | 20/200 | HM | 15 |

TABLE 1 (*Continued*)

| Case No., Age, and Sex | Age at Onset of Diabetes | Age at Onset of Visual Disturbance | Nonproliferative | | | | Proliferative | | | | Preretinal | | | | Vitreous Hemorrhage | | | | Acuities | | | | Follow-up in Months |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | UE† | | TE† | | UE | | TE | | UE | | TE | | UE | | TE | | UE | | TE | | |
| | | | F‡ | L‡ | F | L | F | L | F | L | F | L | F | L | F | L | F | F | F | F | F | L | |
| 30. 56—F | 53 | 55 | 6.5 | 4 | 5.5 | 2.5 | 2 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4.5 | 20/200 | 20/80 | 20/30 | 20/60 | 12 |
| 31. 57—F | 55 | 55 | 5 | 4 | 5.5 | 1.5 | 0 | 2 | 2 | 2 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 4.5 | 20/80 | 20/80 | 20/30 | 20/60 | 15 |
| 32. 48—F | 20 | 41 | 3.5 | 0.5 | 3.5 | 0 | 2 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 4.5 | 0 | 4.5 | 0 | 20/40 | 20/30 | 20/40 | 20/40 | 43 |
| 33. 58—M | 51 | 51 | 3.5 | U | 5.5 | U | U | U | 6 | U | U | U | 0 | U | 0 | U | 4.5 | U | 20/60 | LP | 20/40 | LP | 44 |
| 34. 48—F | 36 | 46 | 3 | U | 5 | 0.5 | 4 | U | 2 | 8 | 0 | U | 4 | 1 | 4.5 | U | 4.5 | 4.5 | 20/30 | HM | 20/40 | 20/60 | 21 |
| 35. 59—M | 54 | 57 | 5.5 | U | 8 | 2 | 3 | U | 2 | 2 | 6 | U | 0 | 0 | 9 | 9 | 0 | 0 | CF | CF | 10/300 | 20/200 | 42 |
| 36. 36—M | 16 | 33 | 0.5 | 1.5 | 5.5 | U | 2 | 5 | 8 | 5 | 0 | 0 | 4 | 4 | 0 | 0 | 4.5 | 4.5 | 20/60 | 20/60 | 20/60 | CF | 20 |
| 37. 62—M | 59 | 61 | 4.5 | 5.5 | 6.5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20/60 | 20/40 | 20/100 | 20/100 | 12 |
| 38. 39—F | 12 | 38 | 1.5 | 0.5 | 2 | 0.5 | 0 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4.5 | 0 | 20/30 | 20/20 | 20/30 | 20/20 | 13 |
| 39. 53—F | 30 | 48 | U | U | 3 | 1 | U | U | 1 | 0 | U | U | 0 | 2 | U | U | 4.5 | 4.5 | NLP | NLP | 20/100 | 20/200 | 21 |
| 40. 53—F | 23 | 48 | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | 20/100 | CF | 20/30 | 10/200 | 30 |
| 41. 47—F | 26 | 46 | U | — | 3.5 | — | U | 8 | 2 | 8 | 6 | 0 | 0 | 6 | 9 | 9 | 0 | 4.5 | 20/100 | CF | 20/25 | 20/200 | 14 |
| 42. 51—F | 31 | 49 | 2 | 2.5 | 2.5 | U | 2 | 6 | 5 | U | 0 | — | 0 | U | 0.5 | 4.5 | 4 | 9 | 20/100 | 20/200 | 20/100 | HM | 27 |
| 43. 54—M | 27 | 51 | 1.5 | U | 2 | 3 | 5 | U | 2 | 4 | 0 | U | 4 | 0 | 0 | U | 5.5 | 3.5 | 20/25 | HM | 20/60 | 20/80 | 26 |
| 44. 56—F | 20 | 55 | U | U | 6 | 4 | U | U | 0 | 0 | 6 | U | 0 | 0 | 9 | U | 0 | 0 | 20/300 | LP | 20/60 | 20/30 | 13 |
| 45. 50—F | 36 | 47 | U | U | 4 | 0.5 | U | U | 6 | 0 | 6 | U | 6 | 0 | 9 | U | 4.5 | 0 | LP | LP | 20/60 | 20/40 | 40 |
| 46. 41—M | 17 | 37 | 5 | U | 2.5 | U | 8 | U | 4 | U | 3 | U | 0 | U | 4.5 | U | 0 | 9 | CF | LP | 20/20 | HM | 12 |
| 47. 58—M | 24 | 55 | U | U | 2 | 0 | U | U | 8 | 0 | U | U | 6 | 0 | 9 | 9 | 4.5 | 0 | CF | CF | 20/25 | 20/25 | 15 |
| 48. 65—F | 52 | 64 | 5 | 6 | 4.5 | 2 | 2 | 2 | 0 | 4 | 0 | 0 | 0 | 4 | 4.5 | 4.5 | 4.5 | 4.5 | 10/200 | 20/200 | 20/60 | CF | 15 |
| 49. 66—M | 62 | 63 | 7 | 3.5 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | CF | 20/200 | 10/200 | 10/200 | 42 |
| 50. 54—F | 10 | 52 | 1.5 | U | 0.5 | 3 | 5 | U | 2 | 0 | 0 | 2 | 1 | 0 | 0 | 9 | 0 | 0 | 20/100 | 20/60 | 20/30 | 20/25 | 26 |
| 51. 38—M | 6 | 36 | 4 | 3 | 2 | U | 8 | 8 | 2 | U | 0 | 3 | 2 | U | 4.5 | 4.5 | 4.5 | 9 | 20/300 | CF | 20/30 | HM | 15 |
| 52. 52—F | 23 | 49 | 3 | U | 2 | 2 | 4 | 6 | 3 | 5 | 0 | 6 | 0 | 2 | 4.5 | 9 | 0 | 0.5 | 20/60 | CF | 20/60 | 20/30 | 15 |
| 53. 61—F | 49 | 60 | 6 | U | 8 | 6.5 | 2 | U | 6 | 5 | 3 | U | 2 | 2 | 4.5 | U | 4.5 | 0 | 20/60 | 20/60 | 20/60 | 20/60 | 13 |
| 54. 53—M | 20 | 51 | U | U | 2.5 | 1 | U | U | 4 | 1 | U | U | 0 | 0 | 9 | 9 | 4.5 | 0 | 20/80 | 20/60 | 20/30 | 20/20 | 12 |
| 55. 62—F | 43 | 59 | 4.5 | 2 | 5 | 0 | 5 | 5 | 6 | 2 | 0 | 0 | 2 | 0 | 4.5 | 0 | 4.5 | 0 | 5/300 | CF | 20/300 | 20/300 | 36 |
| 56. 66—M | 4 | 43 | 2 | U | 4 | 3.5 | 1 | U | 4 | 1 | 0 | U | 0 | 0 | 4.5 | 9 | 4 | 0 | 20/300 | LP | 20/300 | 20/100 | 33 |

* A detailed explanation of the point system used to evaluate data in each of the four classification categories can be found in the body of this article under "Results."
† UE = Untreated eye, TE = treated eye, U = unclassified.
‡ F = Visit before photocoagulation, L = most recent visit.

| | Right eye | Left eye |
|---|---|---|
| A. NONPROLIFERATIVE | | |
| Hemorrhages and/or microaneurysms | | |
| "Hard exudates" | | |
| "Soft exudates" | | |
| Venous abnormalities | | |
| Intraretinal microvascular abnormalities | | |
| Retinal edema (at macula) | | |
| B. FLUORESCEIN | | |
| Arteriovenous phase (15 to 25 seconds) | | |
| Late phase (3 to 5 minutes) | | |
| C. PROLIFERATIVE | | |
| Neovascularization within 1 disc diameter of disc | | |
| Neovascularization, other areas of retina | | |
| Fibrous proliferation within 1 disc diameter of disc | | |
| Fibrous proliferation, other areas of retina | | |
| Plane of proliferation | | |
| Retinal elevation | | |
| D. VITREOUS HEMORRHAGE | | |
| Preretinal hemorrhage | | |
| Vitreous hemorrhage | | |
| History of vitreous hemorrhage | | |
| E. OTHER OCULAR COMPLICATIONS | | |
| Iris neovascularization | | |
| Glaucoma | | |
| Cataract | | |
| Vein occlusion | | |
| Arteriolar abnormalities [1] | | |
| Optic atrophy | | |

Fig. 1 (Krill, Archer, Newell, and Chishti). The Airlie classification, showing the recommended form for recording photographic data.

moderate; and PR extending anterior to the retina's normal position by more than two disk diameters was considered to be advanced.

*Indications for treatment*—In our series, the decision as to which eyes were to be treated was based on the following factors:

1. Bilateral early proliferative retinopathy with preretinal and vitreous hemorrhage in one or both eyes. Generally, the eye with the clearest media was treated.

2. Massive vitreous hemorrhage or widespread advanced proliferative retinopathy in one eye combined with either early or moderate proliferative retinopathy, or advanced localized proliferative retinopathy in the second eye. The better eye was treated.

3. Chronic macular edema with either documented progressive visual loss, or significant visual impairment (20/60 or worse) with no improvement on follow-up.

To minimize variability in technique, all photocoagulation was done by one person (A.E.K.). The Zeiss photocoagulator was used. The second or third intensity on the overload was used with as short an exposure time as possible. The aperture diameter was 4.5 or 6 mm when treating areas outside the macular branches of the superior and inferior temporal vessels, and 3 or 4.5 mm if inside these vessels. We tried to obtain a prominent grayish-white reaction outside the macular branches of the superior and inferior temporal vessels, and a fainter gray reaction within these vessels.

The photocoagulation marks were arranged in a U-shaped configuration with the open end at the optic disk. Two rows of photocoagulation marks were placed outside the macular branches of the superior and inferior temporal vessels. These areas were joined by a double row of photocoagulation marks crossing over the horizontal raphe about 3 or 4 disk diameters temporal to the fovea. In patients with significant macular edema a single row of photocoagulation burns was placed just inside the macular branches of the temporal vessels, in addition to the above-mentioned areas.

This method of photocoagulation included the common sites of neovascularization alongside the major retinal veins, and their primary branches, especially those subserving the macula. Areas of surface neovascularization outside our selected photocoagulation sites were directly photocoagulated. When new vessels extended into the vitreous, photocoagulation marks were placed around their base. New vessels on the surface of the optic disk were usually treated by placing photocoagulation marks close to the disk, avoiding the temporal margin. Small preretinal hemorrhages, when distant from a major retinal vessel, were directly photocoagulated.

Of the 56 patients photocoagulated, 21 required retreatment. At the first treatment, 50 or more photocoagulation marks were placed as described above; on retreatment, fewer photocoagulation marks were necessary.

Initially, all patients were hospitalized, but eventually most patients were treated on an outpatient basis.

Retrobulbar anesthesia was used routinely

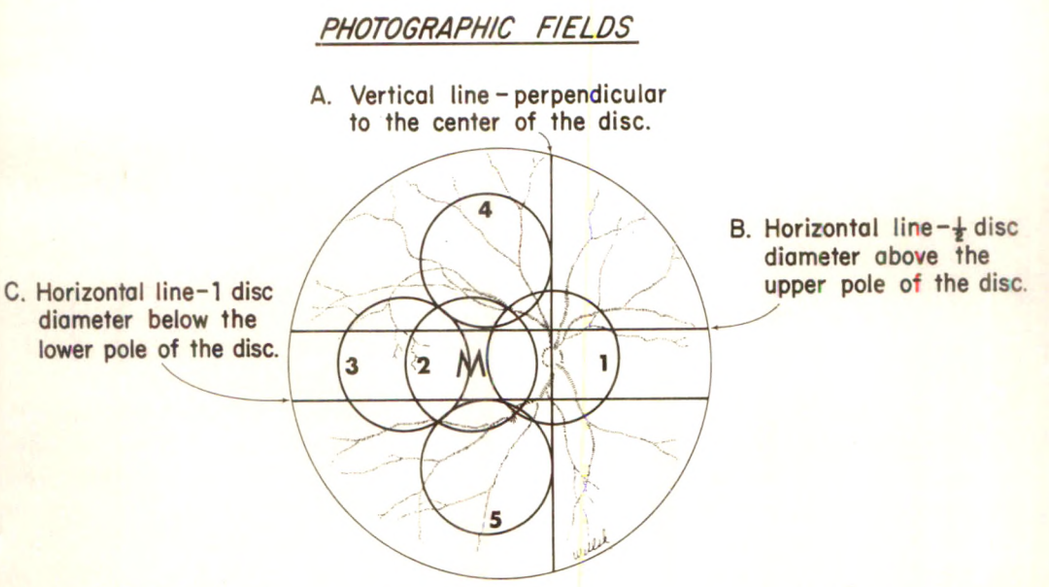



Fig. 2 (Krill, Archer, Newell, and Chishti). Here, the five photographic fields used in the Arlie classification are outlined. Area 1 is centered on the optic disk. Area 2 is centered on the macula. Area 3 has its nasal limit tangent to the macula and is the area covered temporal to the macula. Area 4 includes the region superior to the macula, and Area 5 includes the same region inferior to the macula. The nasal limit of these two areas is tangent to a perpendicular line through the center of the disk. The inferior limit of Area 4 is tangent to a horizontal line one-half disk diameter above the upper pole of the optic disk. The upper limit of Area 5 is tangent to a horizontal line one disk diameter below the lower pole of the optic disk (from Goldberg and Fine[2]).

with initial treatment. When only minimal retreatment was required, anesthesia was often not needed.

## Results

The primary parameters assessed before and after treatment were visual acuity and status of the eyegrounds. Changes in vision of at least two lines on the Snellen chart were considered to be significant, as one-line changes may sometimes reflect variations in testing circumstances.

In evaluating fundi by the Airlie classification (Figs. 1 and 2), we selected what we considered to be the most relevant parameters and weighted each according to our estimate of its importance.

The point total for each fundus area considered was determined by multiplying the Airlie figure (0, 1, 2) by a weighted number (detailed explanation will follow). The total for each category (i.e., nonproliferative, proliferative, preretinal, and vitreous hemorrhage) is the sum of the weighted numbers. These figures are shown for each patient in the table.

Under nonproliferative aspects in the Airlie classification we evaluated intraretinal hemorrhages, microaneurysms, and edema only in the macula, as these findings are of little visual or prognostic significance elsewhere. Each of these parameters was assigned a value of 1. Hard exudates were evaluated in the macula and temporal to this region (Area 3). The temporal location was also evaluated because hard exudates at this site are usually an indication of chronic edema in this area, which ultimately may spread to the fovea. Hard exudates in the macula were assigned a value of 1; temporal to this region, a value of one-half. Venous abnormalities above (Area 4) and below (Area 5) the macula, were given a value of

one-half. Such venous abnormalities may be associated with surface neovascularization, a possible source of preretinal and vitreous hemorrhages.

Neovascularization within one disk diameter of the optic disk, a common site for preretinal and vitreal hemorrhage, was given a value of two. Neovascularization above and below the macula was given one point value. (Neovascularization rarely was found to originate in the macula, and therefore this category was eliminated.) Preretinal hemorrhages in and below the macula were weighted with a value of two. Vitreous hemorrhage was considered to be important in any location; it was given two points at Area 2, one point at Area 1, and one-half point in the other three areas.

The four categories used in the Airlie classification, nonproliferative, proliferative, preretinal, and vitreous hemorrhage, are headings in the table. The total points before and after treatment for each eye are shown under these headings. A designation of "U" indicates that classification was impossible (usually because of vitreous hemorrhage).

Fluorescein data called for in the Airlie classification are discussed elsewhere in this paper under "Specific beneficial effects of photocoagulation," and also in another publication.[3]

In assessing the results of treatment, the patients were grouped in the following manner: 15 patients with early (surface) proliferative retinopathy, 31 patients with moderate to advanced proliferative retinopathy, and 10 patients with nonproliferative retinopathy and macular edema.

*Evaluation of proliferative retinopathy*—A patient was said to have a good result if the treated eye showed an overall improvement or remained static in the proliferative category, while the untreated eye showed deterioration or remained severely abnormal due to extensive vitreous hemorrhage or far-advanced proliferative retinopathy.

*Evaluation of macular edema*—A good result was one in which there was complete or almost complete disappearance of macular edema. This was usually associated with a concomitant resolution of intraretinal hemorrhage and hard exudates.

*Early proliferative retinopathy*—Of the 15 patients with early proliferative retinopathy, eight had good results. In five of these eight cases the retinopathy in the treated eye regressed, while that in the untreated eye progressed. In three of these eight patients, the retinopathy remained static in the treated eye, but deteriorated in the untreated eye. In six other patients with early proliferative retinopathy, photocoagulation did not obviously retard the progression of the retinopathy. The untreated eye in these cases also deteriorated or remained at a state of advanced retinopathy. The one remaining patient in this group showed a more marked improvement of the retinopathy in the untreated eye than in the treated eye.

*Moderate to advanced proliferative retinopathy*—Of the 31 patients with moderate to advanced proliferative retinopathy, 18 had good results following photocoagulation. This group was particularly significant as 11 of the untreated eyes had severely abnormal, mostly unclassifiable retinopathy on both initial and final evaluation. In the remaining 13 patients, three showed deterioration in both eyes, four showed marked deterioration in the treated eye with little change in the untreated eye, and in six cases both eyes remained unchanged.

*Macular edema*—In the 10 patients with macular edema and nonproliferative retinopathy, the principal changes were partial or complete disappearance of edema, exudates, and intraretinal hemorrhage. One patient developed advanced proliferative retinopathy in the treated eye.

### Combined vision and classification data

The visual and classification data of each patient were assessed together to more accurately appraise the effects of photocoagulation.

Results were described as "Good," "Fair,"

"Poor," and "Inconclusive or difficult to assess."

Criteria for a good result was as follows: (1) improvement in vision in the treated eye and deterioration of vision in the untreated eye; (2) improvement of vision in the treated eye with no change of vision in the untreated eye; (3) vision remaining the same in the treated eye with deterioration in the untreated eye; (4) regression of retinopathy in the treated eye and progression in the untreated eye; (5) regression of retinopathy in the treated eye and no change in the untreated eye; (6) no change in retinopathy in the treated eye with marked deterioration in the untreated eye.

A good result based on visual improvement must be accompanied by either improvement in retinopathy or no change in the status of the fundus. Similarly, a good result based on improvement of retinopathy must be accompanied by either improvement of vision or no visual deterioration.

A fair result indicates improvement in either vision or retinopathy. It is distinguished from a good result in that visual improvement may be accompanied by some deterioration of retinopathy, and, conversely, improvement in retinopathy may be associated with slight deterioration of vision.

A poor result is one in which there is a significant deterioration of either vision or retinopathy in the treated eye.

Inconclusive results included cases with improvement or deterioration in either vision or retinopathy in both eyes. In these cases it was difficult to determine the effects of photocoagulation.

The results of treatment were as follows: Twenty-two patients had good results, nine patients had fair results, 15 patients had poor results, and 10 patients had inconclusive results. Of the 10 patients in the last category, seven had improvement in both eyes, and three had deterioration in both eyes. Of the 15 patients with poor results, there were five in which the untreated eye was unclassifiable, both initially and at follow-up. Four patients in this group were legally blind (20/200 or worse) before treatment.

### Specific effects of photocoagulation

Effects on directly treated and adjacent areas are illustrated in Figures 3–12. These effects may be described as follows:

1. New retinal vessels, both surface and those extending slightly into the vitreous, disappeared six to eight weeks after treatment (compare Figs. 3, 4, 6-A and C).

2. Photocoagulation adjacent to the optic disk often caused atrophy of the new capillary vessels on the disk surface. Occasionally, vessels extending into elevated proliferative growths originating from the disk surface also atrophied, leaving only a fibroglial band (Figs. 5-A and B, 6-A through D, 7-B and D).

3. Photocoagulation placed around the base of proliferans extending far into the vitreous often caused atrophy of most or all of the vessels in the proliferative growth (Fig. 8).

4. Waxy exudates and macular edema decreased or occasionally completely disappeared about two to three months after treatment (Fig. 9). Abnormal retinal vessels in the macular area, although not directly treated, became less permeable after photocoagulation to adjacent areas. This is best shown in fluorescein angiography (compare Figs. 10-A and 11-A before photocoagulation with Figs. 10-B and 11-B after photocoagulation).

In patients with macular edema the maximum effect was produced when photocoagulation marks were placed inside and outside macular branches of the temporal vessels and temporal to the macula.

5. There was a general decrease in leakage from abnormal vasculature in both directly treated and untreated areas (see before-and-after photocoagulation photographs in Figs. 3, 4, 10, and 11).

6. Intraretinal hemorrhages often disap-

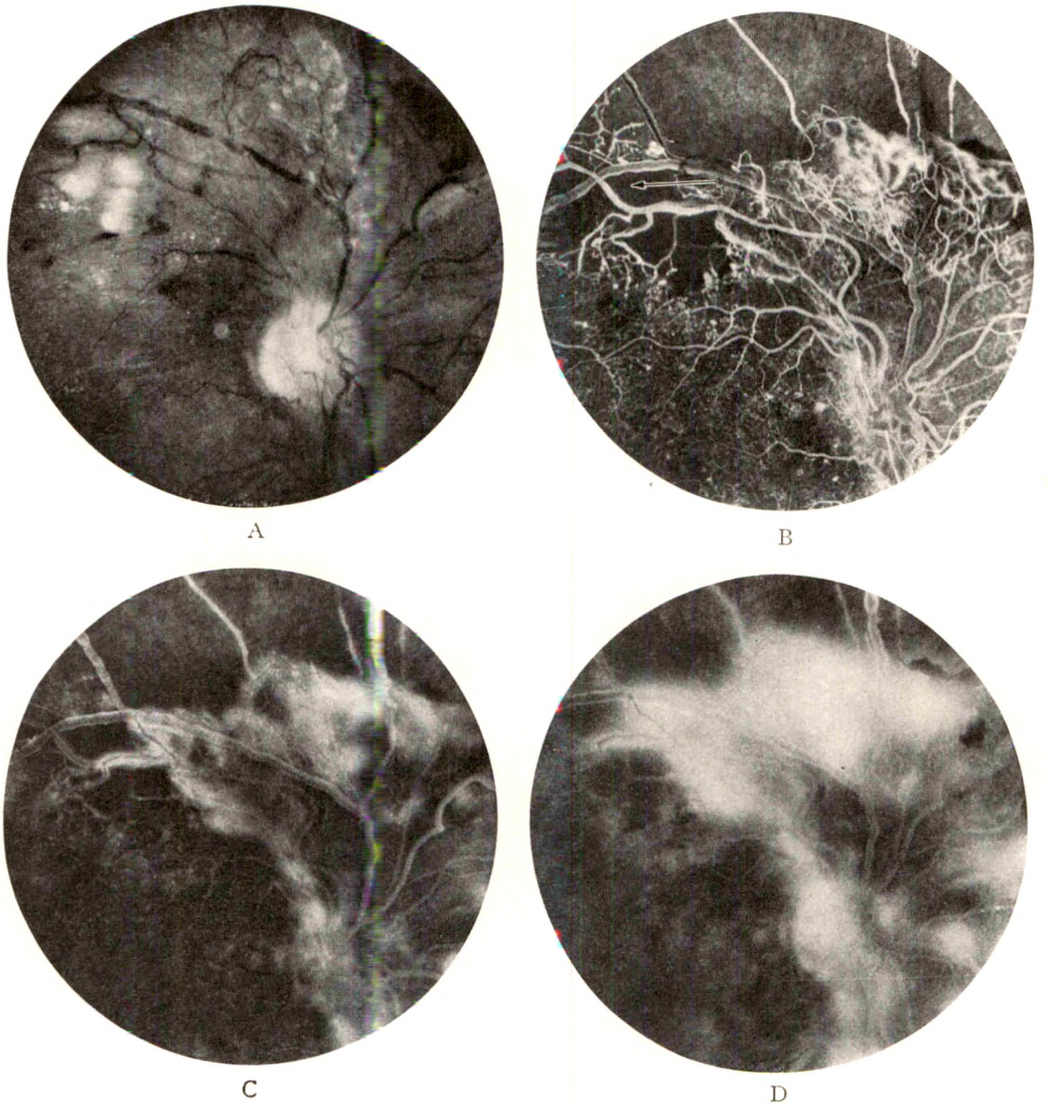



Fig. 3 (Krill, Archer, Newell, and Chishti). Right eye of 45-year-old man before photocoagulation showing (A) control photograph of posterior eyegrounds, and fluorescein angiograms during (B) early and (C) late venous stages, and (D) five minutes after injection. In control photograph (A), note extensive neovascularization superior to disk area and along disk surface. Also note superficial retinal hemorrhages, cotton-wool spots, and waxy exudates. Fluorescein angiograms show widespread areas of capillary nonperfusion, most easily seen during early stages (B and C) of angiography. One such area is indicated by an arrow along superior temporal vessel (B). Extensive capillary dilation, microaneurysms, and shunt vessels are noted in relation to the nonperfused areas. A conglomeration of new vessels, both surface and proliferating into the vitreous, can be seen (B and C) at the upper part of the optic disk extending along the superior temporal vessels. The late angiogram (D) shows profuse dye leakage into the macula and from areas of neovascularization at the optic disk and superior temporal vessels. The superior temporal retinal veins show marked dilation and beading. The vein walls are stained with fluorescein which leaks into the adjacent retina (B, C, and D).

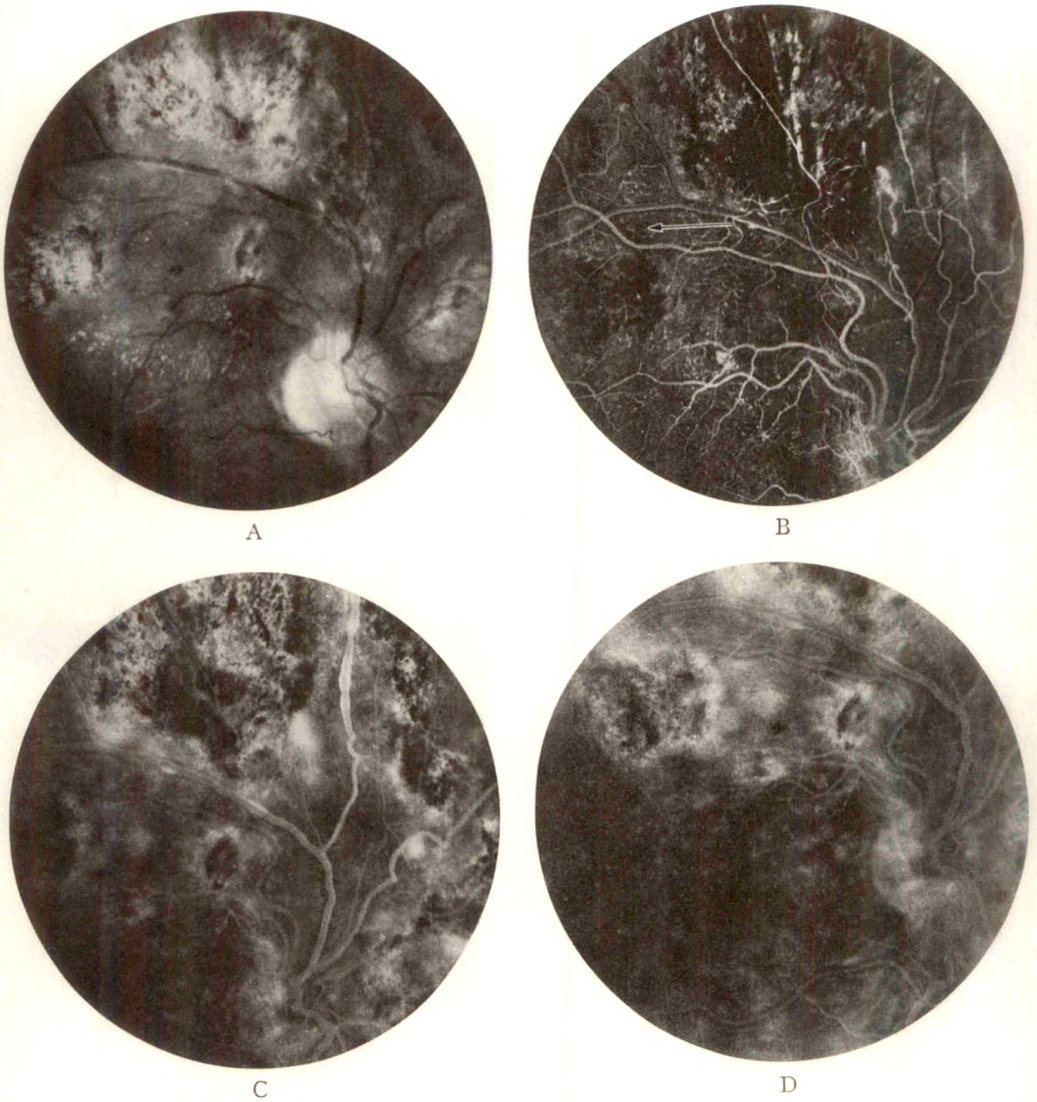



Fig. 4 (Krill, Archer, Newell, and Chishti). Same eye as in Figure 3 shown here five months after photocoagulation. Control photograph (A) may be compared with fluorescein angiograms during (B) early and (C) late venous stages, and (D) five minutes after injection. Note that most of the new surface retinal vessels have disappeared in the superior areas (A, B, and C), both in directly photocoagulated regions and adjacent retina. Most of the hemorrhages in directly treated and adjacent areas have completely disappeared, capillary dilation is now much less evident and the shunt vessels (A and B) are constricted. Many of the capillaries failing to perfuse with dye on previous angiography now appear to be adequately perfused (compare site of arrows in Fig. 3-B and 4-B). There is a dramatic reduction in the area of neovascularization, particularly in the region of the optic disk and along the superotemporal vessels (A, B, and C). Note the considerable reduction in dye leakage in the late angiograms (compare Figs. 3-D and 4-D). There is a marked decrease in caliber of the superotemporal arterioles and veins adjacent to photocoagulation marks (B, C, and D). The superior temporal retinal vein shows absence of beading following photocoagulation, although staining of the vessel wall with fluorescein still occurs (compare Figs. 3-B and 4-B).

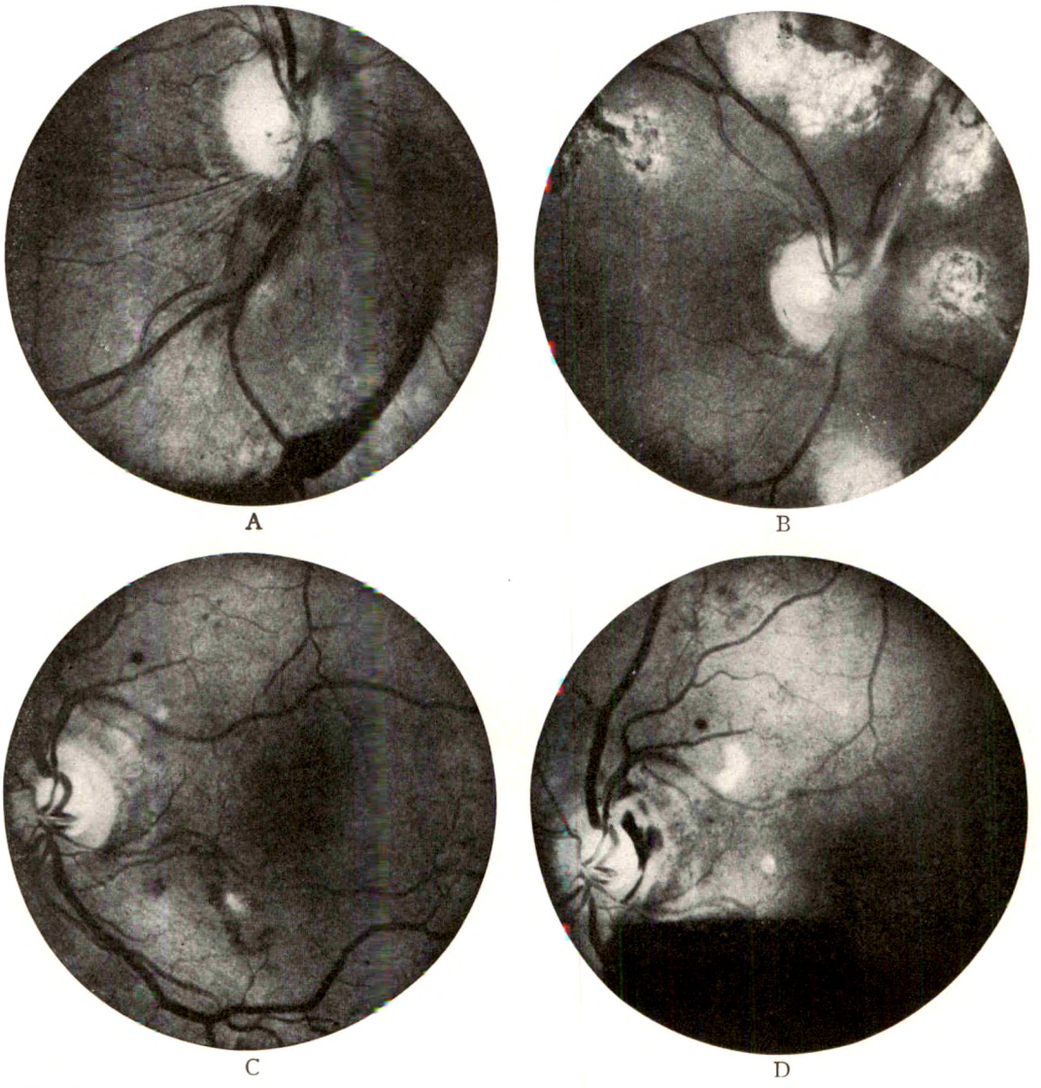



Fig. 5 (Krill, Archer, Newell, and Clashti). Right and left posterior fundi of 45-year-old man (Case 7). Top: Right eye (A) prior to photocoagulation, and (B) seven months after photocoagulation. Bottom: Left or control eye photographed at the same time as treated eye, both before (C) and (D) seven months after right eye had received photocoagulation. There is a considerable decrease in the caliber of the veins and arterioles of the treated eye, whereas in the untreated eye these vessels have remained the same in size. Note disappearance of vessels on surface of right optic disk. Retinal folds temporal to right disk before photocoagulation have disappeared following treatment. Follow-up revealed a preretinal hemorrhage inferior to the optic disk in untreated eye, whereas the treated eye is free from macular edema and hemorrhage.

peared after photocoagulation (Figs. 3, 4, and 6).

7. Microaneurysms, shunts, and areas of capillary dilatation decreased or occasionally disappeared (compare Fig. 10-A with 10-B, 7-A with 7-C, and 3-B with 4-B). Some dilated arterioles and venules also appeared to decrease in caliber.

8. In general, areas of capillary nonperfusion (as demonstrated by fluorescein angiography) failed to reopen following photocoagulation. However, in the macula, some non-

perfused areas did reopen after treatment (compare arrows in Figs. 3-B and 4-B).

9. Many directly treated preretinal hemorrhages partially or completely absorbed within 48 to 72 hours following photocoagulation (Fig. 12-A and B).

10. Photocoagulation marks frequently restricted the spread of preretinal and vitreal hemorrhages, except those originating at the optic disk.

11. Photocoagulation often reduced folds in the retina by causing atrophy of the proliferative fibrous bands producing traction on the retina (Figs. 5 and 8).

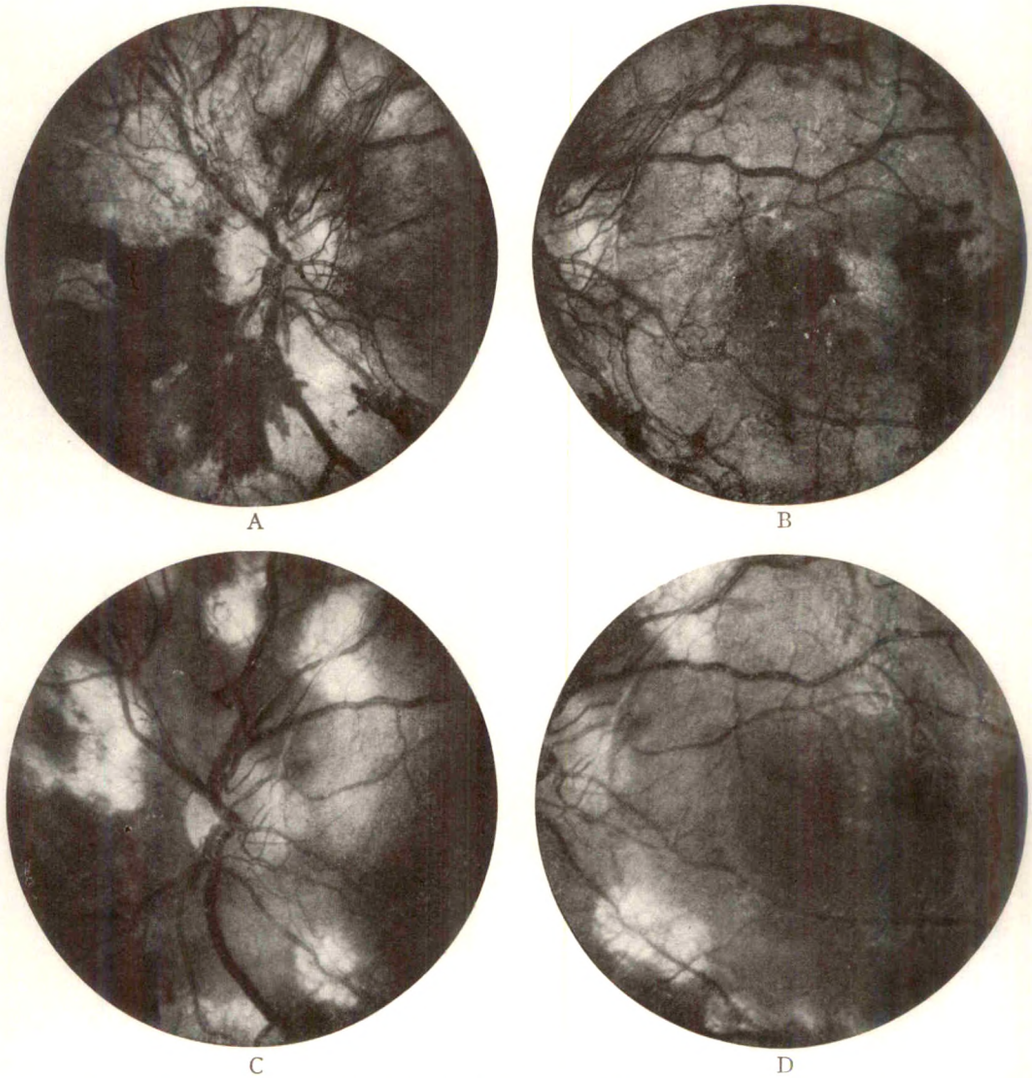



Fig. 6 (Krill, Archer, Newell, and Chishti). Photographs of left posterior eyegrounds and macular area from a 19-year-old diabetic woman before (A and B) and six months after (C and D) photocoagulation. Extensive retinitis proliferans is seen at the optic disk and along the superior and inferior temporal vessels prior to photocoagulation (A and B). These vessels have largely disappeared following treatment (C and D). The retinal vessels show an overall decrease in caliber and most of the hemorrhages have disappeared in areas at or adjacent to the sites of photocoagulation (D).

12. Photocoagulation often prevented the extension of localized detachments by sealing the edges of such areas.

### General effects of photocoagulation

Some of the general effects of treatment were as follows:

1. Reduction in caliber of retinal veins and arterioles was observed (compare inferotemporal vessels in Fig. 5-A and B). Dilated retinal veins occasionally returned to normal size (compare Fig. 3-B with 4-B, and 5-A with 5-B). Segmentation and beading often became less obvious. Retinal venous circulation times improved, but rarely returned to normal.

2. There was disappearance of widespread areas of neovascularization with a replacement by fibrous tissue (Figs. 5, 6, and 7).

3. There was production of a mild optic atrophy and reduction or disappearance of new vessels on the optic disk surface (compare Figs. 8-A and C), even when photocoagulation was not directly adjacent to the disk surface. Extensive disk neovascularization extending into the vitreous was not significantly affected by distant photocoagulation.

### Specific complications of photocoagulation

The specific complications seen in our series of patients are as follows:

1. Inadvertent macular photocoagulation caused visual loss in one patient. The spread of heat from the photocoagulation marks caused a foveal scar. (We have also seen loss of central vision following photocoagulation of the papillomacular bundle in a patient photocoagulated for another disease.[4])

2. Small, spotty visual field defects were frequently noted as a result of receptor damage at photocoagulated sites. Usually patients suppressed such scotomas. Arcuate scotomas reflecting nerve fiber damage were elicited in a few patients.

3. Inadvertent photocoagulation of large retinal veins in two patients resulted in retinal hemorrhage. In one patient treatment had to be completed at a later date.

4. Some patients with vitreous retraction and advanced proliferative retinopathy later developed more extensive vitreous retraction. Perhaps the disease process was accelerated by photocoagulation in such patients.

Two aphakic patients developed posterior vitreal traction at the macula with deterioration of central vision after photocoagulation. One of these patients received less than the usual amount of photocoagulation. Neither had obvious posterior vitreous disease before treatment.

5. Mild iridocyclitis was common, but only of consequence in one patient who developed posterior synechiae. It is important to obtain wide dilation of the pupil before photocoagulation.

6. An effusive retinal detachment of the macula and mid-temporal retina was seen a day after photocoagulation in one patient. Spontaneous absorption of fluid occurred within one week and the patient eventually obtained a good result.

7. New vessels and fibrous tissue occasionally formed adjacent to photocoagulation sites (see arrow in Fig. 10-C). Perhaps this was due to obstruction of small retinal vessels at this site, producing areas of retinal hypoxia.

9. Photocoagulation over an abnormal middle-sized or large retinal vein occasionally produced temporary obstruction (seen on fluorescein angiography). New surface retinal vessels sometimes formed at the margins of such sites, and retreatment was necessary.

Conceivably, photocoagulation of the optic nerve could cause an arcuate scotoma or central visual loss if the papillomacular fibers were damaged. We did not have this complication.

### Causes of poor results

Poor results were obtained in 15 patients in our series. Of these, nine patients had widespread advanced proliferative retinop-

athy and vitreal changes at the time of treatment, causing significant posterior retinal traction. It is doubtful whether most of these patients would be considered for treatment at present. Four patients were considered to have inadequate photocoagulation. One patient did well for two and one-half years and then bled severely from a new proliferative

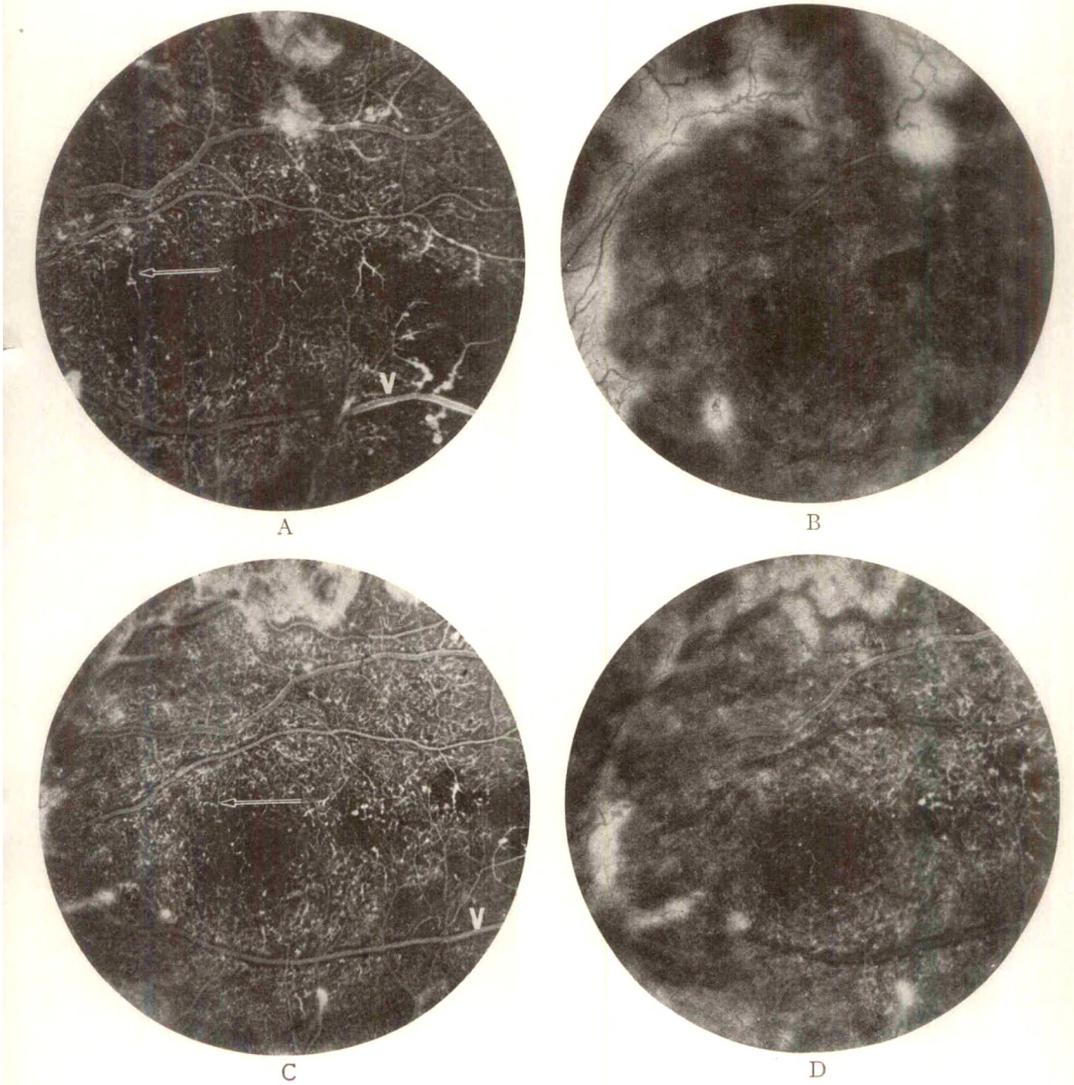



Fig. 7 (Krill, Archer, Newell, Chishti). Fluorescein angiograms of same eye as in Figure 6, shown here before photocoagulation (A and B), and six months afterwards (C and D). Photographs at the left (A and C) were taken during mid-retinal venous phase. Photographs at the right (B and D) were taken three minutes after dye injection. Retinitis proliferans is evident along the superotemporal vessels, which show considerable dye leakage in the late picture (B). Following photocoagulation, there is less retinitis proliferans and reduced dye leakage (D). The details of capillary architecture are more distinct following photocoagulation (compare Figs. A and C). Note many of the capillaries and hairpin-like dilations have disappeared or have become considerably reduced in caliber after photocoagulation (compare arrows in Figs. A and C). The retinal vein walls stain less following treatment, and there is also a reduction in caliber of the venous wall (compare area marked V in Figs. A and C).

site. It is likely that closer follow-up may have been beneficial in this patient. The cause of a poor result in one patient was unknown.

### Precautionary measures in photocoagulation

Based on our experience, certain precautions are advised. These are as follows:

1. High intensities should be avoided. Photocoagulation marks within the macula may cause unexpected foveal or papillo-macular bundle damage when high intensities are used.

2. Photocoagulation should be avoided in patients with advanced proliferative retinopathy and extensive posterior eye-ground traction. Treatment may cause further traction and even hole formation and subsequent retinal detachment.

3. It is questionable whether aphakic eyes should be treated, based on our experience with two patients. If used, photocoagulation should be limited or perhaps divided over several sessions.

4. Treatment should be avoided, if possible, in eyes with extensive vitreous hemorrhage, even though visibility may be adequate. Eyes with blood in the vitreous often require greater intensities to produce adequate photocoagulation. Such intense photocoagulation is more likely to damage the vitreous and lead to eventual retraction. It is best, if possible, to limit the amount of treatment in any eye when more than usual energy is required to produce an adequate burn. Additional photocoagulation can be given at another date.

5. Since vitreous detachment alters the effectiveness of photocoagulation, even in the absence of significant proliferative retinopathy, treatment should be staggered in such areas.

6. One should photocoagulate close to the disk (except, of course, at the temporal margin) in eyes with extensive optic disk proliferation, even if vessels extend far into the vitreous. Atrophy of the vitreal vessels may occur as a result of such treatment. Extensive proliferative retinopathy on the optic disk surface is often the source of additional vitreous hemorrhages after photocoagulation, and may be the most frequent cause of failure of treatment.

7. The amount of photocoagulation used is important. It was soon discovered that in order to significantly decrease macular edema it was necessary to photocoagulate inside, as well as outside, the macular branches of the temporal vessels. It was also noted that photocoagulation temporal to the macula was necessary to eliminate persistent edema and waxy exudates in this region. If not eliminated, edema in this area sometimes spread directly into the center of the macula.

In general, our best results occurred in patients who had extensive photocoagulation, we believe from the elimination of areas of hypoxic retina.

8. Direct photocoagulation of middle and large sized retinal veins should be avoided. As pointed out, hemorrhage may occur at the time of treatment or partial obstruction of these vessels may result, with the formation of new retinal vessels near such sites.

9. Careful follow-up is essential. Even with initially successful results, new retinal vessel growth may continue to form, particularly near the site of previous photocoagulation. Macular edema may also reappear. Additional photocoagulation may be beneficial in such patients. In regard to possible permanent remissions observed in patients followed over long periods, it is our impression that this is more likely to occur with proliferative retinopathy rather than with macular edema, where abnormal retinal vessels may again leak fluid.

## Discussion

In general, our data support the concept that photocoagulation is of greatest value in eyes with early or moderately advanced proliferative retinopathy.[5-14] However, in our experience, this treatment may be of value even in far-advanced proliferative retinopathy, providing it is localized and not associ-

ated with significant posterior retinal traction.

Photocoagulation has both specific and general effects which should prevent or greatly retard future hemorrhagic episodes. These episodes often result in vitreal and proliferative retinal changes with subsequent permanent loss of vision. Furthermore, it is obvious from our data that massive vitreal hemorrhages may take a long time to absorb,

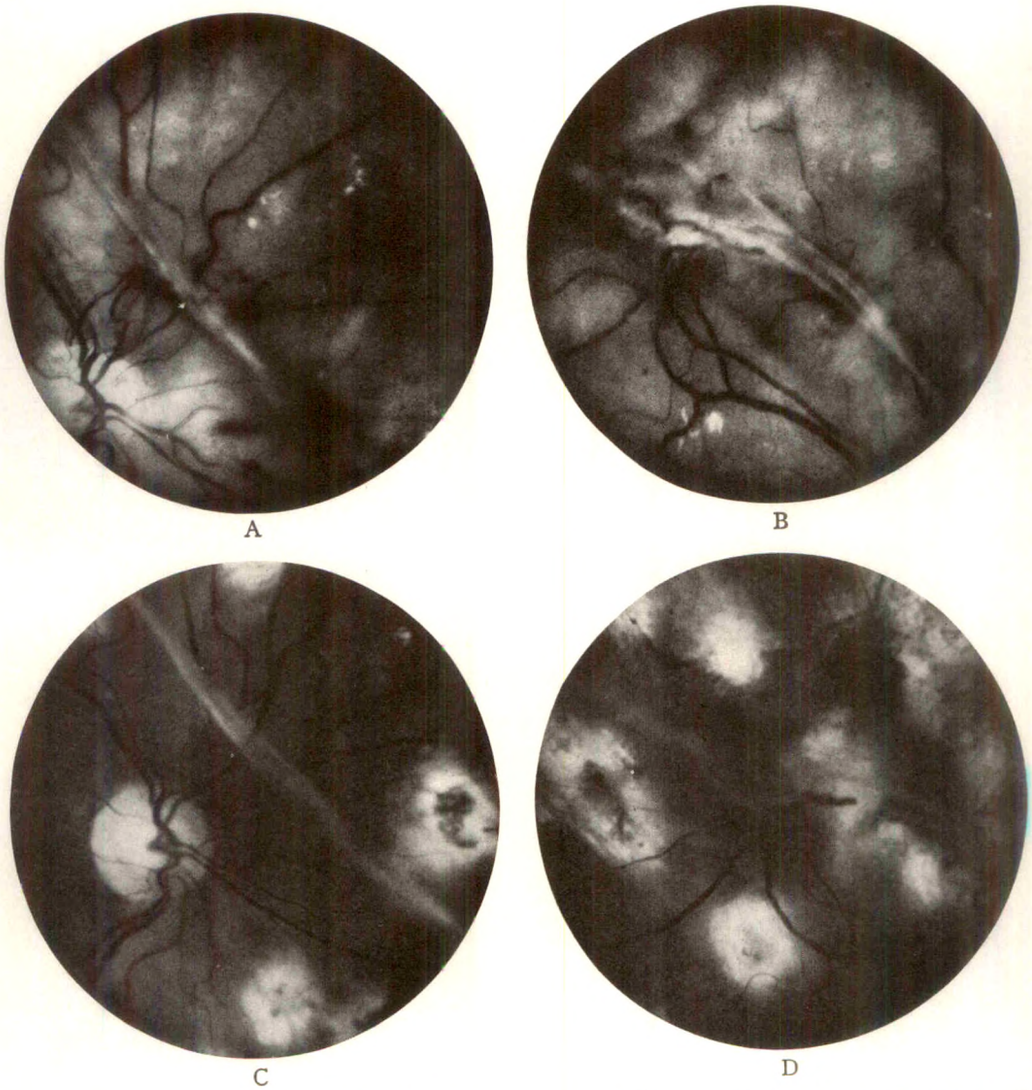



Fig. 8 (Krill, Archer, Newell, Chishti). Photographs of posterior eyegrounds and superotemporal areas of right eye of 47-year-old woman before photocoagulation (A and B) and almost three years afterward (C and D). Note large band-like area of proliferans extending into the vitreous with hemorrhage around and above the proliferative areas (A and B). After photocoagulation, the fibrotic mass is completely devoid of vessels, as the result of photocoagulation of many sites around the base of the proliferative area (C and D). Some of the retinal vessels are significantly reduced in caliber (compare superotemporal retinal veins and arterioles in Figs. A and C), and some of the tortuosity in the superonasal vessels has diminished (compare Figs. A and C). Most new vessels seen (A) on the surface of the optic disk disappeared following photocoagulation (C), although no photocoagulation burns were applied adjacent to the optic disk. Retinal folds present before photocoagulation largely disappeared afterwards.

or may never completely absorb. Only two of 20 untreated eyes, originally unclassifiable because of severe vitreal hemorrhage, cleared sufficiently for later classification. Davis[15] has also commented on the long persistence of large vitreal hemorrhages.

In our experience, proliferative diabetic retinopathy is usually an asymmetrical disease. Only a relatively small number of our patients were considered to have symmetrical proliferative retinopathy when comparing initial classification data. Therefore, patients are often seen with far-advanced disease in one eye and relatively early proliferative retinopathy in the second eye. The justification for treating the second eye is based

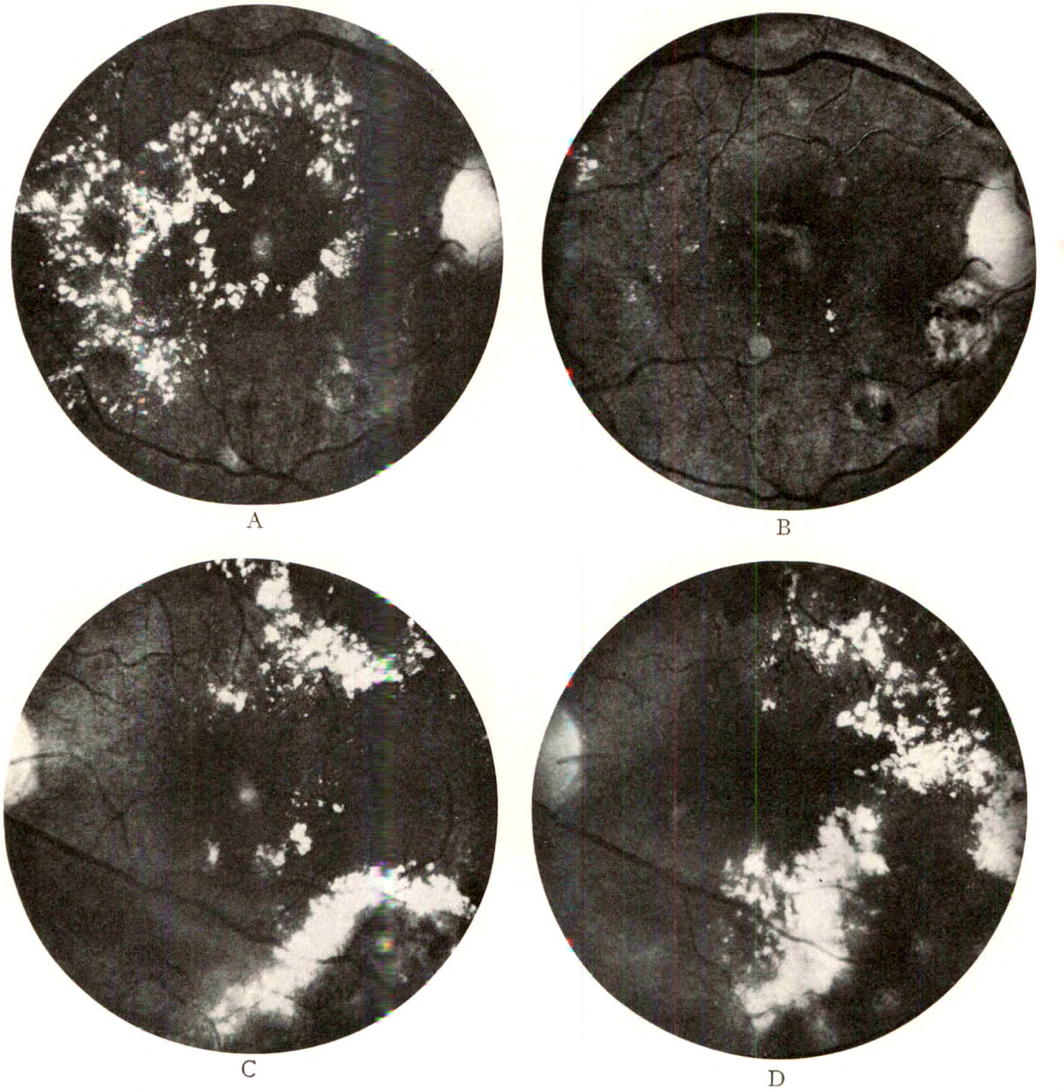



Fig. 9 (Krill, Archer, Newell, Chishti). Right and left posterior fundi of 66-year-old man (Case 12). Top: Treated right eye (A) two weeks after photocoagulation, and (B) 15 months after photocoagulation. Bottom: Corresponding photographs of the left, or control eye. After 15 months, most waxy exudates have disappeared in the treated eye (B), whereas after this lapse of time, there is an increase in the number of waxy exudates in the untreated eye (C and D). Macular edema almost disappeared in the treated eye.

on data indicating that once one eye has far-advanced disease, the other eye often follows the same course.[16]

Several other factors favor treatment of certain eyes with early proliferative retinopathy (PR):

1. Several long-term studies indicate that eyes with PR do not do well.[15,17-20] Approximately 50 to 60% of the eyes with early PR are blind (20/200 vision or worse) within five years and few retain normal vision.

2. In general, eyes with PR near the disk do worse than those with PR elsewhere.[18] Fifty percent of eyes with PR near the disk are blind in two to three years, whereas 50% of the eyes with PR elsewhere are blind in five years. At sites distant from the disk, surface vessels occasionally show spontaneous regression.

3. The older the patient is, the worse his prognosis with either proliferative,[16,18-22] or nonproliferative retinopathy.[19,23,24]

4. Visual prognosis after a vitreous hemorrhage is particularly dismal. Even after the first vitreous hemorrhage, one-third of such eyes are permanently blind within one year and another one-third have permanently impaired vision.[19]

It seems, then, that eyes with PR most likely to benefit from treatment are: (1) those from older patients (beyond the age of 40), (2) those with vessels near the optic disk, (3) those with a past or present vitreous hemorrhage, or (4) the fellow eye of patients with a severe vitreous hemorrhage or far-advanced PR in the other eye.

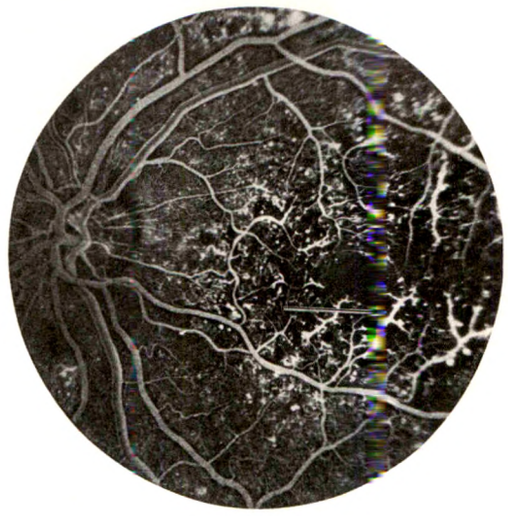
The average follow-up in our series of 56 patients is only two years; however, some published data on the natural course in eyes with PR which can be used for comparative purposes are:

1. In one study[16] it was shown that patients severely blind in one eye (20/200 or worse vision) frequently become blind in the remaining good eye (defined as 20/80 or better initial vision in this study) in a relatively short period of time. Among 17 of our patients whose treated eyes had good vision (20/80 or better), six (35%) with blind fellow eyes eventually had visual acuity of 20/200 or worse in their treated eye during follow-up periods which averaged 24 months. In the study cited,[16] where no treatment was given, 59% of the good eyes became blind within one year.

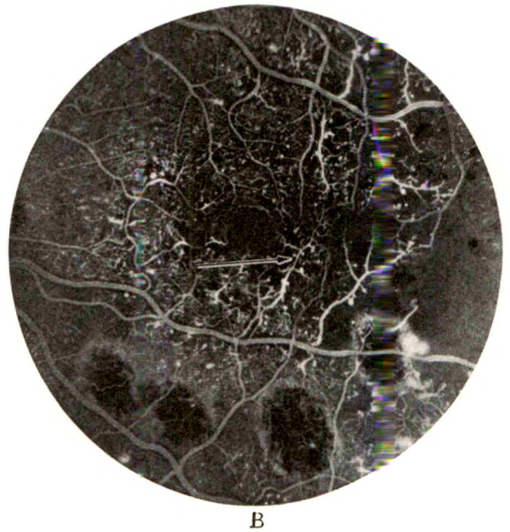
2. Deckert, Simonsen, and Poulsen[18] noted that 46% (12* out of 26 patients) of eyes with pre- and peripapillary proliferation went blind (20/200 vision or less) within two years of follow-up. Twenty-seven percent (7 out of 25 patients) of the eyes we treated in this category went blind upon follow-up (a period averaging close to two years).

3. Beetham[17] reported data from two-year and longer follow-up periods in eyes with initial vision of 20/40 or better in patients over 20 years of age. The exact number of eyes could not be calculated from the data given in the paper. After two years, 20% of the eyes had less than 20/200 vision, and in another 20% vision was between 20/50 and 20/200. Of our 20 eyes in this category, five (25%) had worse than 20/200 vision and four (20%) had vision between 20/50 to 20/200. However, the average age of our group (46 of our 56 patients were 45 years or older) may have been considerably higher. (We could not determine how many of Beetham's patients were in this age range.) It has been shown that in eyes with PR the long-term visual prognosis is considerably worse in those who are 40 years of age or older than it is for a younger age group.[17-19,21] Furthermore, valid comparisons between eyes should probably include classification as well as visual acuity data. It is of interest that in several other series of photocoagulated eyes where vision initially was 20/40 or better, one-year follow-up studies revealed 53 to 76% of the treated eyes

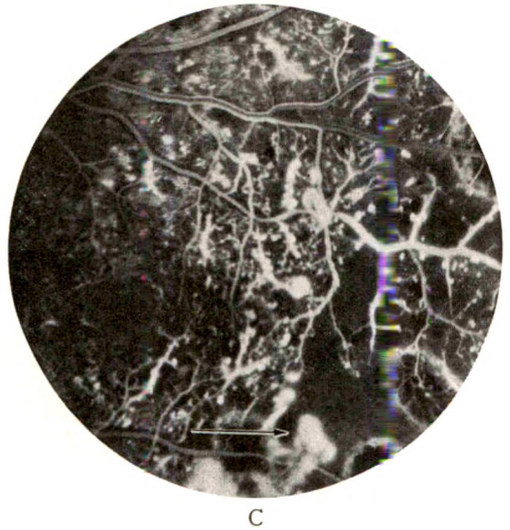
* Figure 3 of the original publication indicates that three eyes were blind when originally seen and therefore these were eliminated from this calculation.



A



B



C

kept this vision.[25] In our series 53% maintained 20/40 vision or better.

The claim that only five-year data are valid in evaluating treatment[25] is questionable when referring to eyes with PR. This is true particularly where the second eye is already severely blind,[16] of eyes with vitreous hemorrhage,[19] and of eyes with proliferative retinopathy near the disk,[18] as it has been pointed out that blindness occurs in many of these eyes within one or two years after initial evaluation.

Most important in this type of study was the comparison of both visual acuity and classification data from treated and untreated eyes on follow-up. Such evaluation indicated that 31 eyes definitely benefited from photocoagulation. In seven patients, both the treated and untreated eyes did well; therefore, it is uncertain that treatment was of any value in these patients. It is difficult to compare our data with that of other workers, since there are few series in which one eye alone was treated. Okun[26] published data

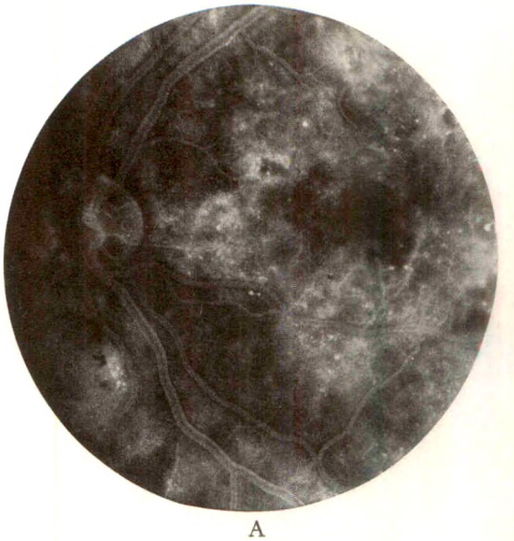
Fig. 10 (Krill, Archer, Newell, Chishti). Fluorescein angiograms of the left posterior eyegrounds of a 28-year-old diabetic woman. The angiograms were taken during the midretinal venous phase in all photographs: (A) before photocoagulation, (B) three months afterwards, and (C) six months afterwards. Note the dilated and irregular capillaries in the macula and surrounding areas before photocoagulation. Typical dilated hairpin-like shunt vessels (arrow points to one) are frequently associated with areas of nonperfused retina. The major retinal veins and arteries are dilated and many microaneurysms are evident. Three months after photocoagulation (B), the retinal capillary architecture is more regular. The capillaries, shunt vessels, and microaneurysms are all reduced in size, although there is no obvious change in the number of microaneurysms present. The hairpin-like capillary dilations are less obvious (compare arrows in Figs. A and B). Six months after photocoagulation (C), the capillary architecture is again indistinct and microaneurysms are again prominent. Dye leakage is again seen (even more than before photocoagulation) from several dilated capillaries and microaneurysms, particularly near sites of photocoagulation (see arrow at bottom of Fig. C).

from 50 patients where one eye only was treated. In 25 patients, there was no change of status in either eye. In the other 25 patients, progression occurred in 23 untreated and two treated eyes.

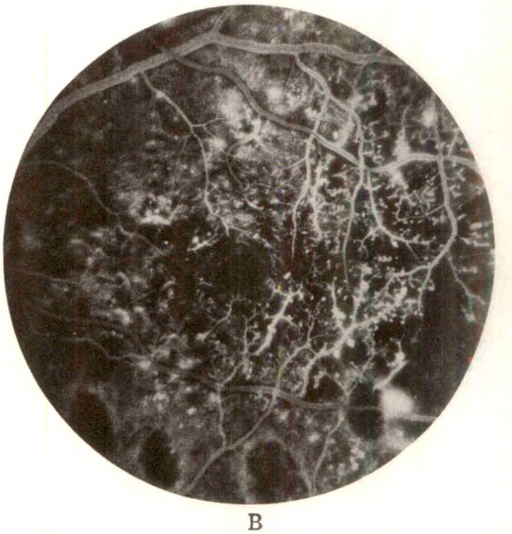
In contrast to our experience with PR, patients with no or minimal PR and bilateral macular edema often had symmetrical involvement. At first, visual results were poor in many patients with bilateral macular edema. However, the visual results improved when we photocoagulated inside the macular branches of the temporal vessels and temporal to the macula, in addition to the routine sites. All patients treated in this latter manner have shown at least partial absorption of macular edema, although vision has not improved in some because of permanent damage to the fovea, particularly as a consequence of cystoid degeneration.

We particularly favor treatment of older diabetic patients with chronic bilateral macular edema, since spontaneous resolution is unlikely after the age of 40.[19,23,27] In general, we follow patients with macular edema until progressive visual loss can be adequately documented, or where, in eyes with vision of 20/60 or worse, we establish that there are no signs of improvement within two to four months. It should be emphasized that the longer macular edema persists, the greater the likelihood of permanent macular damage.

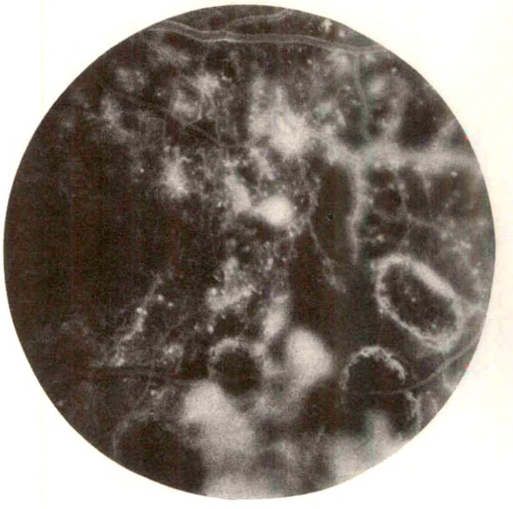
We have only treated diabetics with nonproliferative (simple or background) reti-



A



B



C

Fig. 11 (Krill, Archer, Newell, Chishti). Same eye as shown in Figure 10. All photographs were taken three minutes after dye injection: (A) before photocoagulation, (B) three months afterward, and (C) six months afterward. There was considerable decrease in dye leakage throughout the macular area three months after photocoagulation (B), with better visualization of small vessel architecture. Six months after treatment (C), vessel details are again blurred with considerable dye leakage evident, particularly adjacent to sites of photocoagulation.

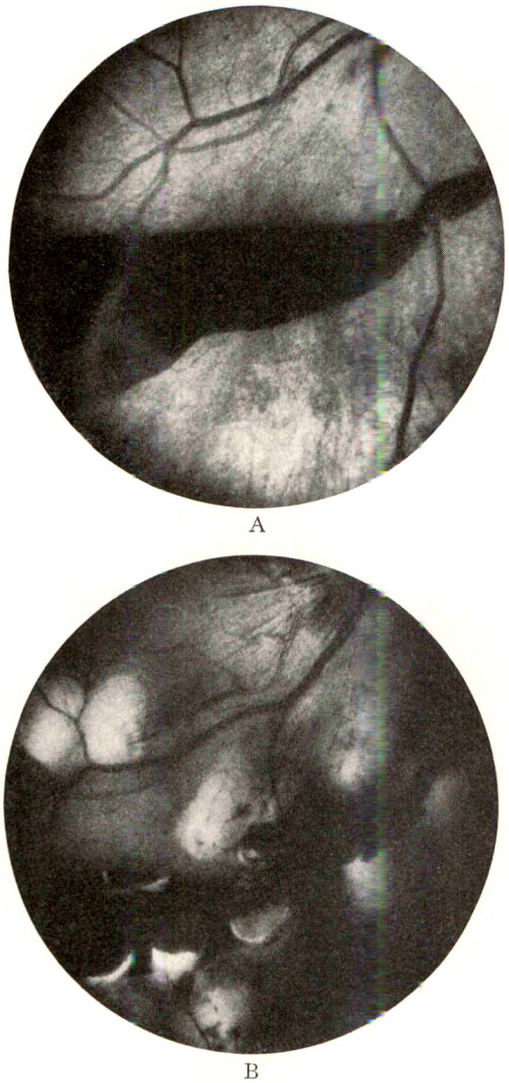


Fig. 12 (Krill, Archer, Newell, Chisati). Photograph at site of pre-retinal hemorrhage in 48-year-old man (A) before photocoagulation and (B) 24 hours later. A considerable portion of the hemorrhage has disappeared after direct photocoagulation.

nopathy for chronic macular edema. Because of the favorable natural course in many of these patients,[19,23,27-30] it is questionable whether such eyes should be photocoagulated. In fact, in one study 61% of eyes with nonproliferative retinopathy were unchanged visually after 10 years.[28] Visual prognosis is worse in eyes with hemorrhages and exudates than in eyes with only microaneurysms.[28] Also, as indicated previously, the prognosis is worse with age.

On the other hand, some eyes with simple diabetic retinopathy progress to proliferative diabetic retinopathy.[15,30] At present, it is uncertain which eyes are likely to show such progression. Furthermore, some workers[31-33] feel that there is a predisposition toward either proliferative or nonproliferative retinopathy and that these are separate entities. Data which may support this latter notion are the findings that glaucoma and a positive response to topical corticosteroids are more common in patients with nonproliferative retinopathy than in the normal population, but in patients with PR there is the same incidence as in the normal population.[34]

Probably the two most important beneficial effects of photocoagulation are the elimination of neovascularization on the retinal surface and a decrease in permeability of small intraretinal vessels.

Neovascularization on the retinal surface or extending only slightly into the vitreous is usually eliminated by direct photocoagulation of such areas, or at times, of adjacent retina. New vessels extending more into the vitreous cannot be directly treated with the xenon instrument, but these vessels may decrease in number or even disappear when photocoagulation is placed around the base of such areas. New vessels on the optic disk surface or elsewhere may atrophy even when treatment is quite distant. However, this does not occur with extensive proliferation extending significantly into the vitreous. Photocoagulation in such instances may be placed around the base of such areas, as pointed out, or adjacent to the optic disk if this site is involved.

A pronounced decrease in permeability of smaller intraretinal vessels, best demonstrated by fluorescein angiography, occurs after photocoagulation. Leakage of fluorescein from abnormally dilated capillaries and shunt vessels in both directly treated and adjacent retinal areas was sometimes considerably reduced by photocoagulation. This is true even if these vessels persist after treat-

ment. Persistent vessels are usually reduced in caliber.

Decrease in leakage from intraretinal vessels in the macula and reduction in their caliber is most likely secondary to the diminished blood supply requirement of and reduced venous return from destroyed retina. A decrease in the pressure head of venous return ultimately should cause a reduction in the size, and probably the permeability, of small vessel radicles. Possibly, the destruction of hypoxic areas may also have reduced the production of or eliminated tissue metabolites with local toxic effects (such as increased permeability and dilation) upon the retinal vasculature.

Wide ranging changes after extensive photocoagulation were demonstrated. These general effects included disappearance of surface retinal vessels at sites distant from photocoagulation, such as on the optic disk surface, reduction in caliber of large retinal veins and arterioles, and frequently mild optic atrophy concomitant with arteriolar attenuation. The changes in the large retinal vessels, like those in the small retinal vessels, may also be secondary to some extent to diminished blood supply required and reduced venous return from destroyed retina. However, this reasoning does not explain attenuation of larger retinal vessels, which may occur in untreated as well as treated retinal quadrants. It is obvious that it is not necessary to photocoagulate along retinal arterioles, as previously claimed, to produce arteriolar attenuation and optic atrophy in patients with diabetic retinopathy.

The atrophy of surface retinal vessels at sites a considerable distance from photocoagulation, such as on the surface of the optic disk, may be due to the elimination of an abnormal chemical factor speculated to originate in hypoxic tissue, which is converted to anoxic tissue. The possibility of a vasoformative factor originating in hypoxic tissues has been previously suggested.[35-37] The disappearance of new vessels after treatment suggests that such a factor may aid in maintaining new vessels as well as stimulating their original formation. Strong support for the existence of a chemical factor in hypoxic tissues comes from the notation of the disappearance of new vessels on the surface of the iris after photocoagulation in one patient with diabetic retinopathy and in another with a branch vein occlusion.[4]

The beneficial effect of reducing the amount of retinal tissue to supply with a presumably limited circulation is also suggested by observations that diabetic retinopathy is less frequent or less severe in patients with a reduction in actively metabolizing retinal parenchyma. For example, it is known that severe PR is rare in eyes with myopia over five diopters, in eyes with advanced glaucoma, in eyes with severe chorioretinitic atrophy, or in eyes with a retinal degeneration.[28,34,38,39]

Photocoagulation is probably contraindicated in patients with advanced PR where there is significant vitreoretinal traction, since the procedure may hasten progression of the disease. Furthermore, on the basis of our limited experience, less photocoagulation should be used in the treatment of aphakic patients with diabetic retinopathy, since it appears that vitreous retraction in the macular area is more likely to occur in such patients.

In general, our best results were obtained with extensive photocoagulation. Direct treatment of only proliferative areas was not enough. In such cases, new surface retinal vessels continued to form and generalized effects were lesser in degree, or not noted. It is recommended that photocoagulation should destroy not only obvious proliferative sites, but in addition, destroy retina considered unimportant for visual purposes. The beneficial effects of such treatment were demonstrated in this report. The results of inadequate treatment in patients with chronic macular edema was also discussed.

Careful follow-up of treated patients with diabetic retinopathy is important for several reasons. First of all, the full effect of extensive photocoagulation may not be noted for up to four months after treatment. Secondly,

certain changes may necessitate retreatment. Fresh areas of retinitis proliferans and surface neovascularization may occur adjacent to areas of photocoagulation, probably as the result of venous obstruction, stasis, and hypoxia with renewed stimulus to new vessel growth. This finding was most frequent where a photocoagulation scar occurred directly over or adjacent to a large retinal vein, compromising blood flow in the vessel. Finally, some patients with previously resolved macular edema may again start to leak from dilated capillaries and shunts in the macula within six to 12 months after initial treatment. Retreatment may be beneficial in such patients. Also, on occasion, dilated capillaries and shunts which had atrophied reappeared in such patients.

It appears on the basis of our experience to date, that "permanent" remissions occur more commonly in patients in whom PR is the sole reason for treatment. Such patients may be hastened into the final atrophic stage by photocoagulation, supposedly the end stage of many untreated eyes with PR.[40] On the other hand, the problem of permanently diseased, leaky, small intraretinal vessels in the macular area of treated patients with macular edema remains, and possibly such patients will never have a permanent "cure" after photocoagulation.

The most frequent cause of a poor result in patients with early PR was the eventual development of an extensive proliferative growth on the optic disk surface. Perhaps extensive photocoagulation, including treatment adjacent to the nasal half of the disk, prevents this occurrence. Only a few patients treated in this manner have developed significant proliferation on the disk surface. Therefore, we now routinely photocoagulate patients with PR nasal to the optic disk.

Hopefully, the argon laser, which photocoagulates vessels that are not in contact with the retinal surface, can be used to treat many of the eyes with extensive vasculature a sufficient distance above the retina that have not responded to photocoagulation. Preliminary data in this area are encouraging.[41]


## Summary

Data are presented from 56 patients with diabetic retinopathy who were followed for one year or more after photocoagulation of one eye only. On the basis of visual acuity and changes in classification in the treated eye, 31 of these patients had some benefit from photocoagulation. Fifteen patients did poorly. Ten of these had advanced proliferative retinopathy. Four were thought to have had inadequate photocoagulation. (The necessity for extensive photocoagulation in most patients is stressed.) One patient had insufficient follow-up, and the importance of adequate follow-up is emphasized, particularly in patients with macular edema.

Ten patients had inconclusive results. In seven of these, both treated and untreated eyes did well, and three had deterioration in both eyes. No conclusions regarding the effects of photocoagulation were possible in these patients.

Photocoagulation has both local and widespread effects. Probably the two most important effects are the elimination of areas of surface proliferation and a general decrease in the permeability of small retinal vessels.

The possibility of a chemical factor existing in hypoxic tissues causing the formation and maintenance of new vessels, even at distant sites, is suggested. It is speculated that photocoagulation converts hypoxic to anoxic tissue, presumably eliminating such a factor.

Photocoagulation, if used properly, is of definite value in certain patients with early and moderately advanced proliferative diabetic retinopathy, and in certain patients with chronic macular edema.



## Acknowledgment

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# OPHTHALMOSCOPIC MONITORING OF OXYGEN THERAPY IN PREMATURE INFANTS

## Fluorescein Angiography in Acute Retrolental Fibroplasia

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Retrolental fibroplasia (RLF) was first described by Terry[1] in 1942. In the early 1950s, studies by Patz[2] in the United States, Ashton and associates[3] in England, and Gyllensten and Hellstrom[4] in Sweden demonstrated a toxic effect of oxygen therapy in premature infants. With this discovery there followed a period of curtailment of oxygen administration in the premature nursery and the almost complete elimination of RLF. During this period of restricted oxygen therapy, infant mortality associated with respiratory distress,[5,6] as well as the incidence of cerebral palsy,[7] was increased. It has since been shown[8–10] that infants with respiratory distress syndrome frequently require a high concentration of oxygen for survival. In the past several years, pediatricians have tended toward a more liberal use of oxygen in managing this problem. As a result, there may be an increase in the incidence of RLF.[11]

About 10% of infants born before 37 weeks' gestation develop the respiratory distress syndrome in the neonatal period; this is the most common cause of death in newborn infants. Standard practice has been to administer oxygen to these infants only when clinically indicated by cyanosis, retraction, or other signs of respiratory distress. Fetal hemoglobin can carry more oxygen than adult hemoglobin; thus, clinical recognition of hypoxia is more difficult in the newborn. Cyanosis might not be noticed in an infant until oxygen saturations of 75-85%,[12] which corresponds to an arterial oxygen tension of 32-42 mm Hg on the fetal hemoglobin dissociation curve. On the other hand, an infant can appear pink and have an arterial oxygen tension lying between 80 and 400 mm Hg due to flattening of the fetal dissociation curve at its upper end. Ideally, oxygen administration is also monitored by serial measurements of arterial oxygen tensions. Such methods require special personnel and laboratory facilities, repeated arterial punctures or indwelling arterial catheters, and involve risks.[13,14] Compounding the problem is the fact that the upper limit of a safe range of arterial oxygen tension before irreversible retinotoxicity is not presently known.

Because of these difficulties, it was suggested that the ophthalmologist might provide an additional guideline in oxygen therapy by serial ophthalmoscopic monitoring of retinal vessel caliber.[15] Experimental[3,16,17] and clinical[18–21] observations suggested that retinal vasoconstriction appeared to be the earliest sign of hyperoxygenation. In an effort to test the feasibility of this suggestion, the present study was undertaken.

### Materials and Methods

Daily, over a 10-month period beginning in August of 1969, all infants receiving oxygen in the premature nursery of Jackson Memorial Hospital were ophthalmoscopically examined. The indirect ophthalmoscope was used, permitting examination without opening the incubator. The examiner could simply

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introduce his arms through the portals of the incubator, holding the lens with one hand and immobilizing the infant's head and hands with the other (Fig. 1). A self-retaining infant eyelid speculum was used, when necessary, to hold the eyelids apart. Care was taken to prevent undue pressure on the globe (Fig. 2). Dilitation of the pupil was effected with 1 or 2 drops of 1% cyclopentolate HCl (Cyclogyl) and 2.5% phenylephrine HCl (Neosynephrine) applied at one hour and then one-half hour before examination. In a few infants, an increased number of apneic episodes were associated with ophthalmic examination, despite the utmost care on the part of the examiner.

Whenever possible, the ophthalmoscopic examinations were performed at the same time that arterial oxygen tension determination was being made. Retinal vessel caliber was graded as normal, dilated, or slightly, moderately, or markedly constricted. In selected cases, arterial specimens were drawn for oxygen tension determinations after the ophthalmoscopic examinations to determine if they correlated with the clinical impressions. When an infant's oxygen therapy was discontinued, ophthalmoscopic examination was performed once a week. Following discharge, the infant was re-examined in two to three months, and thereafter, as indicated.

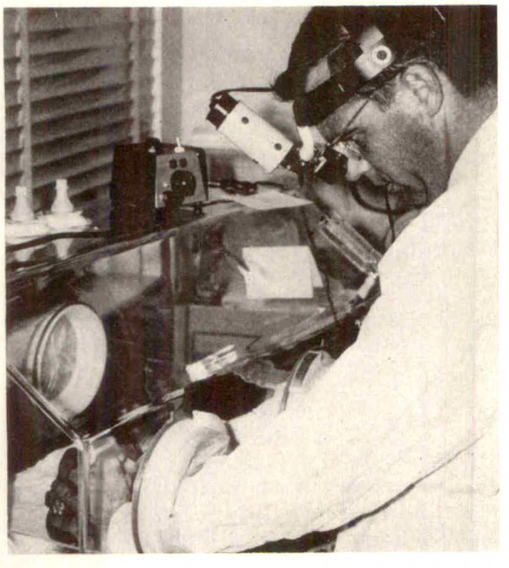


Fig. 1 (Cantolino and associates). Technique of indirect ophthalmoscopy.

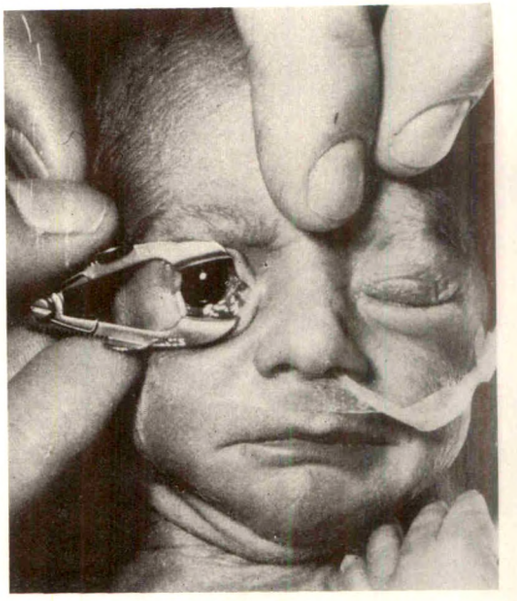


Fig. 2 (Cantolino and associates). Insertion of the infant eyelid speculum.

Whenever the clinical condition of the infant permitted, fundus photographs were taken to document the ophthalmic examination, using the Kowa fundus camera. Fluorescein fundus angiography was also performed on several premature infants, utilizing the Zeiss fundus camera (Fig. 3). For each of these studies, 0.3 ml of 5% fluorescein was injected intravenously.

Overall, a total of 102 infants were observed. Color fundus photographs taken on 68 occasions on a total of 29 infants and fluorescein angiography performed on 17 occasions on nine infants (Table 1).

## Results

Quite early in the study it became apparent that persistence haze made it impossible to visualize the fundus even with the indirect ophthalmoscope in many of the smaller prematures. This haze persisted for as long as four weeks after birth, followed by a period

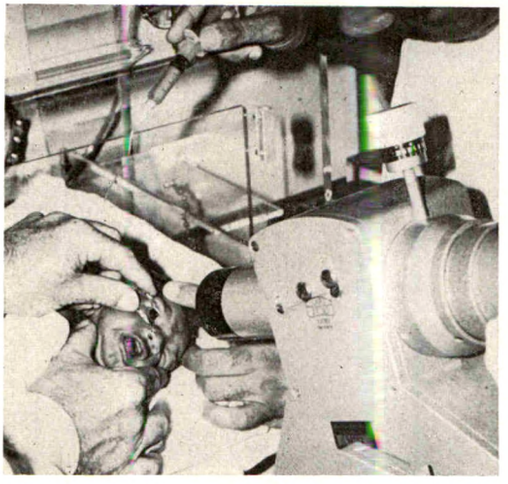


Fig. 3 (Cantolino and associates). Technique for performing fluorescein fundus angiography.

of gradual clearing. In general, it appeared the smaller the premature, the greater the incidence of haze and the longer it persisted (Table 2). Portable slit-lamp examination revealed the cornea and lens to be quite clear, excluding these two tissues as a cause of the haze. A persistent anterior tunica vasculosa lentis could often be visualized as multiple arcades of looped vessels in the pupillary space (Fig. 4). In several postmortem specimens obtained from very small infants, the hyaloid system extending into the tunica vasculosa lentis could be demonstrated (Fig. 5). We suggest that the persistence of this hyaloid system in very immature newborns may account in part for the presence of this haze.

In the course of this study we had occasion to follow three infants with respiratory distress syndrome who manifested a dense impenetrable haze during much of the time they received oxygen, thus precluding any possibility of effective funduscopic monitoring. Each of these infants went on to develop acute and then cicatricial RLF. The clinical course of these infants is as follows:

TABLE 1

CLINICAL MATERIAL

| Birth Weights | No. Infants |
|---|---|
| Under two pounds four ounces (1000 g) | 19 |
| Two pounds four ounces to three pounds five ounces (1000–1500 g) | 29 |
| Three pounds six ounces to four pounds seven ounces (1500 to 2000 g) | 42 |
| Over four pounds seven ounces (2000 g) | 12 |
| Total | 102 |
| Fundus photographs | 29 (68*) |
| Fluorescein angiography | 9 (17*) |

* No. occasions procedure performed.

## CASE REPORTS

*Case* 1—Baby boy B had a birth weight of two pounds two ounces. Shortly after birth he was started on oxygen therapy was administered by mask, with the ambient concentration in the isolette varying between 28 and 54% during this period of time. For the first 10 days, the media were too hazy to visualize any fundus details, including the disk. By 11 days of age, the haze had begun to clear sufficiently so that the disk could just barely be seen. Oxygen therapy was discontinued when the child was two weeks of age, and at three weeks of age, a reasonable view of the retinal vessels was obtained for the first time. A significant degree of tortuosity of the arterioles and some dilitation of the veins was observed. Subsequent observations of this child revealed the progressive changes of acute RLF with large, tortuous, arterial trunks going out to the temporal periphery and ending in multiple, proliferative, branching arcades extending up to, but not beyond, a sharply delineated gray border of unvascularized retina. Fluorescein angiography was performed in the nursery when this infant was two

TABLE 2

PRESENCE AND DURATION OF IMPENETRABLE HAZE IN INFANTS OF VARIOUS BIRTH WEIGHTS

| | Under 1000 g | 1000 to 1500 g | 1500 to 2000 g | Over 2000 g |
|---|---|---|---|---|
| % with haze | 78% (15/19) | 41% (12/29) | 26% (11/42) | None |
| Duration | 3–35 days | 1–10 days | 1–3 days | — |

and one-half months of age, and it revealed vascular proliferation temporally and extensive leakage of dye in the area of the arcades. This infant has gone on to develop cicatricial changes with temporal detachment of the retina (Fig. 6).

*Case* 2—Baby boy R had a birth weight of two pounds four ounces. Because of respiratory distress, this infant was given oxygen by mask in his isolette over the first 18 days of life. The ambient oxygen concentration in the isolette was recorded as varying between 25 and 44% during this period, with the highest concentrations recorded over the first week of life when the infant's clinical status was most unstable. For the first eight days of life, this infant's media were too hazy to visualize the retinal vessels adequately. Over the next seven days, with gradual clearing in the media, progressive changes of acute RLF could be observed. Fluorescein angiography performed at one month of age revealed arcades of vascular proliferation extending temporally and ending abruptly at the gray zone of unvascularized retina (Figs. 7 and 8). These showed lighting up and leakage of dye in a pattern reminiscent of the sea fans described by Welsh and Goldberg.[22] This infant, also, has gone on to develop cicatricial changes of RLF.

*Case* 3—Baby boy, one of twins, had a birth weight of two pounds 14 ounces. Shortly after birth, because of respiratory distress, oxygen was administered by mask in concentrations of 34 to 50% over the first two days of life. Because of progressive deterioration in his clinical status, the infant was placed in a Bird respirator at the end of his second day of life. While on the respirator, periodic arterial oxygen tension determinations were made. These varied between 40 and 370 mm Hg. By five days of age, the infant's condition had stabilized and he was taken off the respirator and given oxygen by mask in concentrations of 30 to 36% until eight days of age, when all oxygen therapy was discontinued. Subsequently, the baby's course was unremarkable. Because of extremely hazy media, the fundus could not be visualized until seven days of age. At that time, vessel caliber was evaluated as normal to slightly dilated. Unfortunately, early serial fundus photographs could not be taken in this case, but from two months of age onward his retinal changes were documented photographically. This infant, also, went on to develop severe cicatricial changes of RLF, but in his right eye only (Fig. 9). The asymmetry of involvement is interesting in this case; the left fundus appeared essentially normal at the time severe cicatricial changes were present in the right eye.

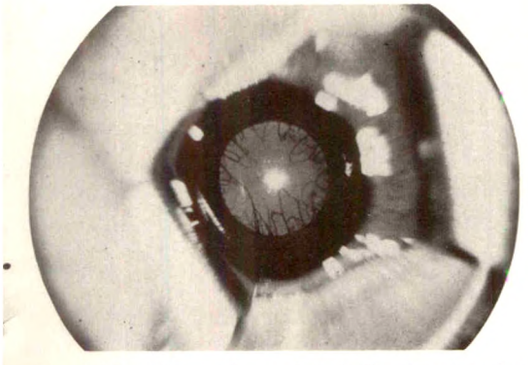


Fig. 4 (Cantolino and associates). Persistent tunica vasculosa lentis.

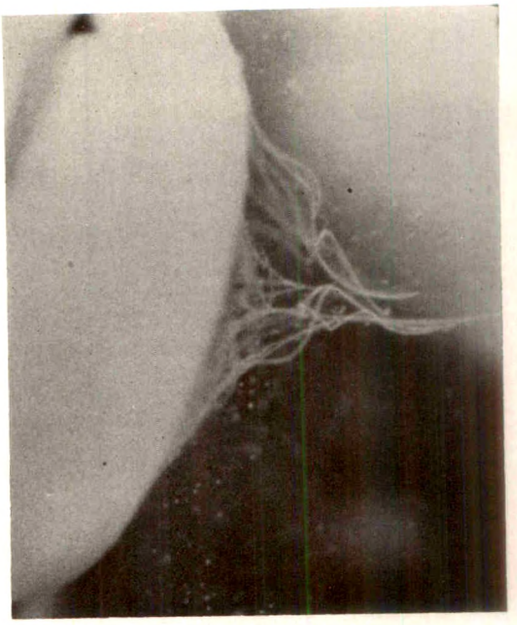


Fig. 5 (Cantolino and associates). Hyaloid arteries stalk.

## Comment

When hazy media was not a problem in these premature infants, it soon became apparent that clinical evaluation of retinal vessel caliber presented another area of difficulty in ophthalmoscopic monitoring. Independent attempts by three observers to estimate the presence of hyperoxia on the basis of constricted retinal vessels proved to be remarkably inaccurate (Table 3). In the course of this study there were 50 instances where a concomitant arterial oxygen tension value was available for comparison with the ophthalmoscopic evaluation of retinal vessel caliber. In 23 instances where the retinal vessels were judged to be of normal caliber, there were five occasions when the arterial oxygen tension

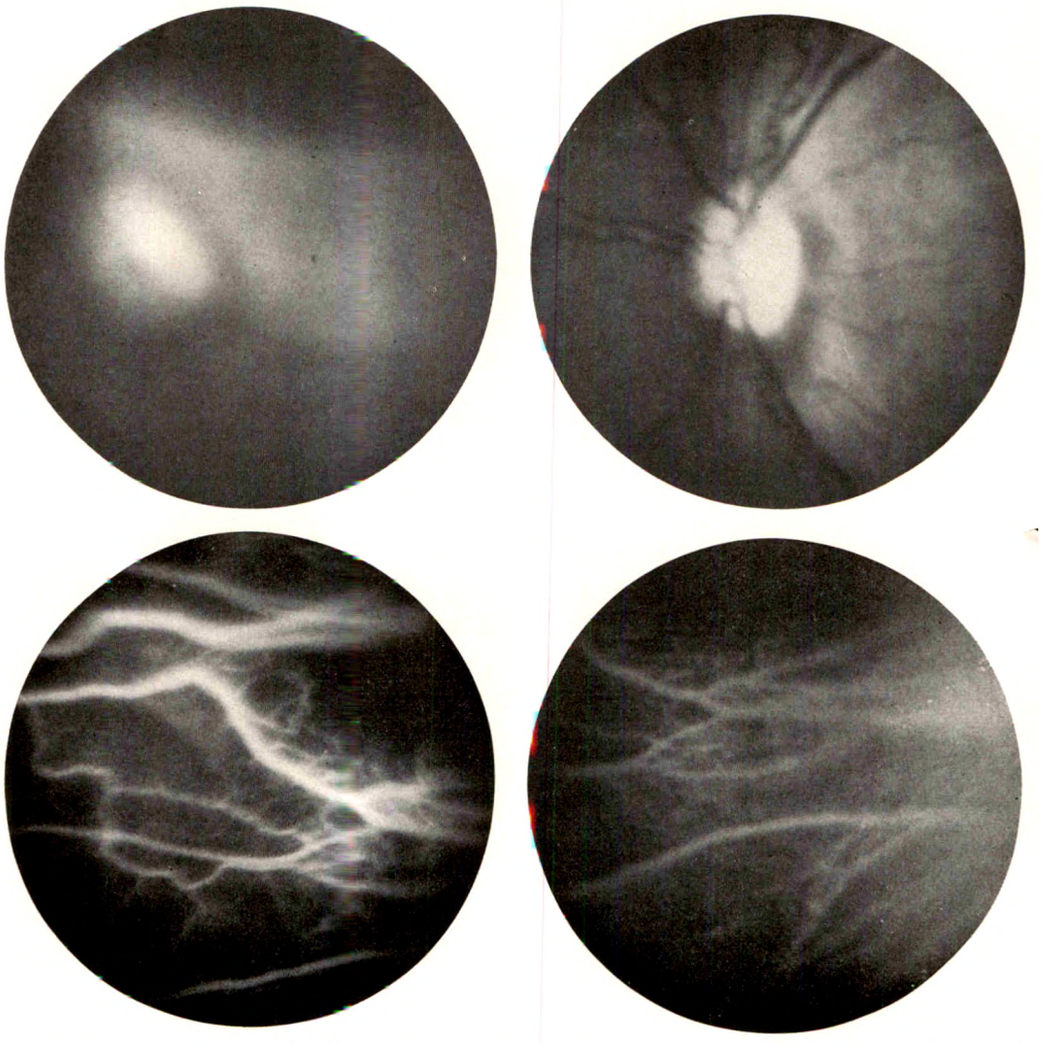


Fig. 6 (Cantolino and associates). Case 1. Top left: Age 15 days. Top right: Age 44 days. Bottom left and right: Fluorescein angiography, temporal periphery, age two and one-half months.

was 150 mm Hg or higher, with one as high as 400. Three of these arterial oxygen tension determinations were made on temporal artery specimens and the remainder were umbilical artery specimens. In 27 instances where retinal vessels were described as constricted, only three had arterial oxygen tension values greater than 150 mm Hg, with a fourth of 122 mm Hg, while the remainder were all under 70. Nine of these determinations were made on temporal artery samples, one on a radial artery sample, and the remainder were obtained from the umbilical artery. Right-to-left shunting of blood through the ductus arteriosus may make umbilical artery specimens less well oxygenated than radial or temporal artery specimens, which probably more accurately reflect the degree of oxygenation in the retina. In several of these infants with apparent constriction of vessels and extremely low umbilical artery oxygen tension values, the clinical signs of severe

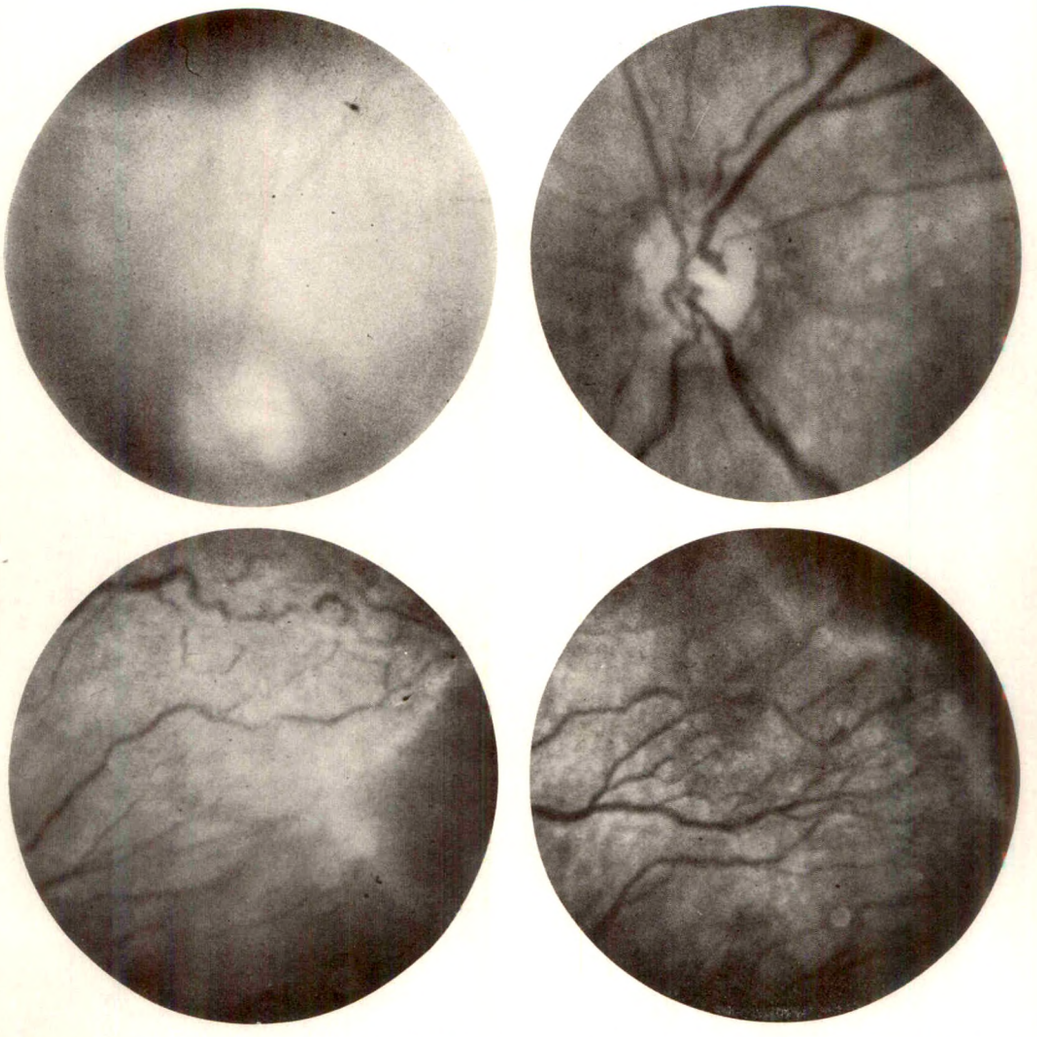


Fig. 7 (Cantolino and associates). Case 2. Top left: Age 10 days. Top right: Age two months. Bottom left and right: Temporal periphery at age two months.

respiratory distress, including cyanosis, appeared consistent with the arterial oxygen tension values. Photographic documentation of this poor correlation of arterial oxygen tension and retinal vessel caliber was obtained (Fig. 10). Retinal vessels frequently appeared quite narrow in infants of about 2¾ pounds (about 1300 g) or less during the first week of life, particularly when such infants were ill or in severe respiratory distress, regardless of the arterial oxygen tension.

## Discussion

The results of this study would seem to indicate that the proposed method of monitoring oxygen therapy by ophthalmoscopy has some serious problems: (1) the existence of hazy media in a significant number of infants at the time they need oxygen, and (2) poor correlation of ophthalmoscopically evaluated retinal vessel caliber and arterial oxygen tension values in many smaller, distressed premature infants.

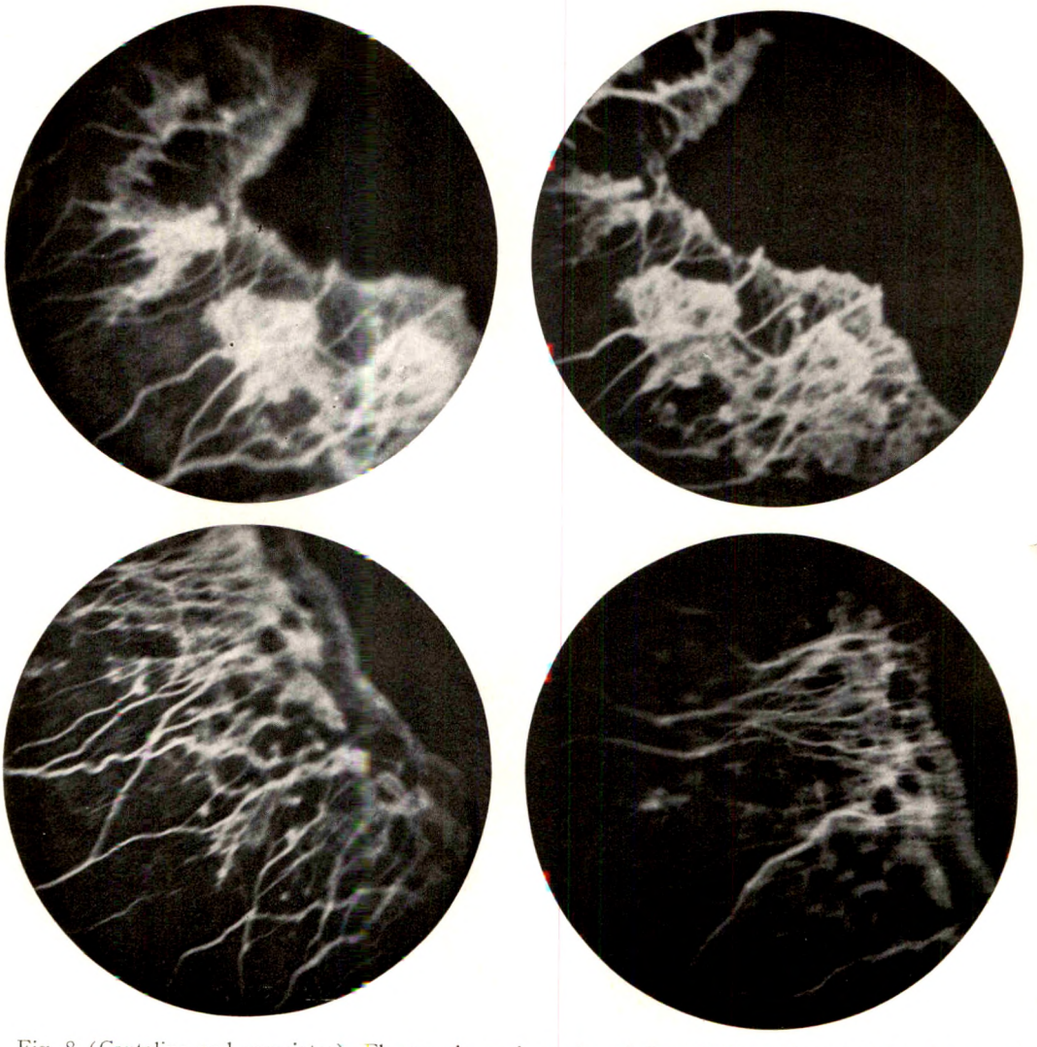


Fig. 8 (Cantolino and associates). Fluorescein angiography of Case 2. Top left and right: Temporal periphery at age two months. Bottom left and right: Temporal periphery at age two and one-half months.

The presence of hazy media in premature infants has been noted by other observers, but it has not been reported as significant an obstacle to ophthalmoscopy as we found it to be. It has been stated that in most instances where this haze is impenetrable to direct ophthalmoscopy, it could usually be penetrated with the brighter illumination of the indirect ophthalmoscope. We did not find this to be the case in a significant number of premature infants with low birth weights. While the mortality rate is highest among these low-birth-weight infants, it is the survivors of this group who require the most oxygen for the longest periods of time and who are therefore at greatest risk of developing RLF. This is supported by numerous studies, including the cooperative study of 1956[23] which showed an inverse relationship between birth weight and incidence of RLF. A survey conducted in 1967 by Silverman[24] concluded that 82% of all cases of RLF occurred in infants under three and one-half pounds (1500 g), and most of these were under two pounds six

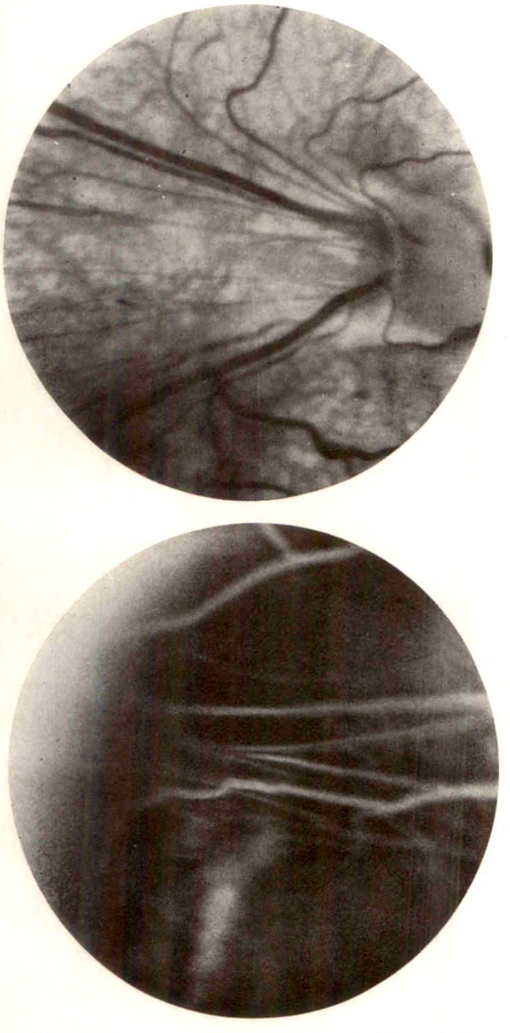


Fig. 9 (Cantolino and associates). Case 3. Top: Age two months. Bottom: Fluorescein angiography, temporal periphery (age two months).

ounces (1100 g). A recent retrospective study by Kalina[25] showed an incidence of RLF of 7% in premature infants weighing under two pounds 14 ounces (1300 g) at birth and an incidence of only 0.1% in those weighing more than this. Thus, while 80 to 90% or more of cicatricial RLF is occurring in premature infants under three pounds, we found that about 60% of this weight group have impenetrably hazy media for intervals of one day up to a month after birth.

Retinal vasoconstriction is well documented as a consequence of hyperoxygenation in extensive experimental work.[3,16,17,26] Clinical studies demonstrating this same vasoconstriction with hyperoxygenation in premature infants include reports by Huggert,[19,20] Patz,[18] and Lamotte.[21] In these clinical reports, however, there are no arterial oxygen tension values given to support the implication that all of these instances of constricted vessels represented concomitant hyperoxia. While it is established that hyperoxygenation is one of the causes of retinal vessel vasoconstriction, we contend that in small, sick, premature infants, evaluation of retinal vessel caliber is as a sign of hyperoxygenation is fraught with difficulty and is often misleading. We have documented this in showing apparent vessel narrowing with hypoxia in some of these infants. This narrowing of vessels in hypoxic infants may in fact represent reflex vasoconstriction, observed in other animal species, which tends to centralize the circulation of blood in the brain and heart when the newborn is subjected to stresses such as acidemia, hypothermia, hypovolemia, or even hypoxemia. We did note that several infants manifested a degree of vessel narrowing which occurred with hyperoxygenation. It was, however, too subtle to be clinically useful. This is demonstrated by a five-pound two-ounce infant whose narrowing of retinal vessels could not be appreciated on clinical observation, but when fundus photographs of this child at the normal and high levels of arterial oxygen tension were compared side by side, it could be

TABLE 3

COMPARISON OF ARTERIAL $PO_2$ (IN MM HG) WITH CONCOMITANT RETINAL VESSELS DESCRIPTION

| | |
|---|---|
| Normal | 22–24–30–35–39–45–50–50–51<br>54–54–58–62–62–67–68–76–93<br>150–165–242–250–400 |
| Constricted | 10–21–30–30–32–35–36–48–49<br>50–50–54–60–60–60–65–66–67<br>68–70–70–75–85–122–150–160–290 |



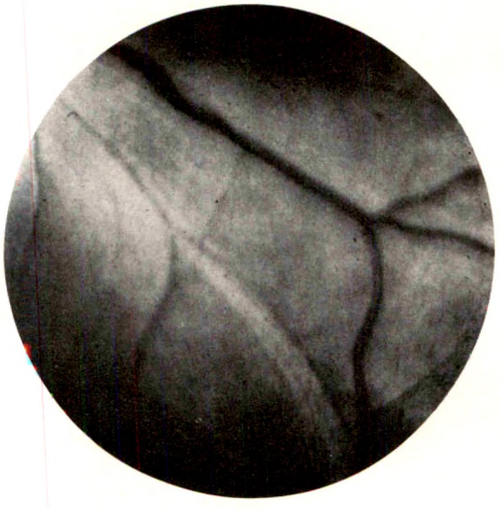


Fig. 10 (Cantolino and associates). Top: Arterial oxygen tension 400 mm Hg. Bottom: Same patient as above, now breathing room air.

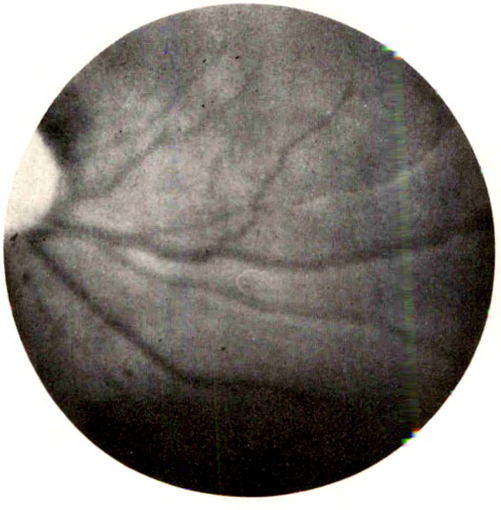




Fig. 11 (Cantolino and associates). Top: Arterial oxygen tension 242 mm Hg. Bottom: Same patient as above, now breathing room air.

seen that there was narrowing with hyperoxygenation (Fig. 11).

On the basis of this work, we contend that our pediatric colleagues should not be lulled into a false sense of security because an ophthalmologist is in attendance in the premature nursery; we were of no assistance in preventing RLF, and they will have to continue their efforts at maximum clinical surveillance of these infants, utilizing frequent, periodic arterial oxygen tension values as a guide, until a practical means for constant monitoring of arterial oxygen tension becomes available. While we believe that it is not feasible to monitor oxygen therapy ophthalmoscopically, the suggestion to try was an excellent one. We are presently extending our fluorescein fundus angiographic studies of these infants in hopes of adding another dimension to the study of the natural history of this disease process. When more is known about the course of this retinopathy, it might

become possible to use cryotherapy or photocoagulation to interrupt or to modify its development before severe cicatricial changes ensue.

## Summary

Daily ophthalmoscopic monitoring was performed on 102 premature infants to test the feasibility of such monitoring as a guide to oxygen therapy. This monitoring was unsuccessful because of hazy media and the extremely small caliber of the retinal vessels. Fundus photography and fluorescein angiography were performed on selected infants to demonstrate the acute lesion of retrolental fibroplasia.

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# INVERSE RETINITIS PIGMENTOSA, DEAFNESS, AND HYPOGENITALISM

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The hereditary retinal abiotrophies are a group of disorders in which the common pathologic feature is a primary degeneration of the outer layers of the retina. In many cases hereditary abnormalities of other organs are found, and numerous syndromes have been described.[1]

This paper presents studies of a family in which three siblings demonstrate inverse retinitis pigmentosa, neurosensory hearing loss, and a dysfunction of the pituitary-gonadal system of a type previously not described in association with ocular pathology.

## FAMILY HISTORY

One brother and two sisters were studied; there were no other siblings. The family was Jewish; the parents were first cousins, as were the maternal grandparents. All members of the three preceding generations (Fig. 1) originated in the same area in Eastern Russia. The only married sibling (Case 3) has no children.

Although no other family members were available for study, many had had ophthalmologic and general examinations. The maternal grandmother (II-1), age 90, is reported to have glaucoma, but no other ocular abnormalities are known, nor any symptomatic eye disease. A first cousin (IV-2) is reportedly deaf, and has a son (V-1) with a hearing defect; neither has any visual difficulty. Another first cousin (IV-1) was mentally retarded and died in an institution. There is no known family history of any gonadal or other endocrine disturbance.

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## CASE REPORTS

*Case* 1—This 62-year-old man (D.K.) noted the onset of a slowly progressive hearing loss at the age of 11 years. He first experienced blurring of central vision at age 20. There had been no previous ocular disease. Attempts were made initially to improve vision with glasses and vitamins, but they were not successful, and the visual impairment progressed slowly to reach a stable end point eight to 10 years later. There has been no further subjective loss of vision in the past 30 years, and he denies any impairment in night vision or color vision. The development of secondary sex characteristics (i.e., facial and pubic hair) began at age 14 and progressed normally. He denies impotence. There are no known systemic illnesses.

General physical examination was within normal limits, but the testes were small and soft. Laboratory examination of the blood and urine was normal, and the VDRL was nonreactive. X-ray films of the chest and skull were normal.

Otologic examination showed a moderately severe neurosensory hearing loss, with no demonstrable abnormalities of the canals or tympanic membranes.

Ocular examination revealed a central visual acuity of hand movements at three feet, both eyes. Midperipheral vision was finger counting at three to five feet, and eccentric viewing was prominent. Retinoscopy showed an error of −1.00 sph. ⊂ +0.50 cyl. ax. 90, both eyes. Ocular motility was full and normal. Slit lamp examinations of the adnexa and the anterior segments were normal, and the pupils were equal and reacted well to light. Applanation tensions were 18 mm Hg, both eyes. There was moderate nuclear sclerosis of both lenses and both showed small posterior subcapsular opacities centrally. In the right eye, the vitreous was clear, but in the left, there was a marked asteroid hyalitis. Examination of the fundus revealed multiple amorphous and "bone-corpuscle" pigment deposits confined to the posterior pole of both eyes. No abnormal pigment was seen anterior to the equator. There were well-circumscribed, mottled, yellowish lesions in both macular areas, approximately 1.5 to 2 disk diameters in size. No foveal light reflex could be seen, and there were a few small pigment deposits within the macular lesions. The vessels were narrowed with vascular sheathing more prominent around the arterioles. The disks were somewhat pale with distinct margins and small, shallow central cups. (Fig. 2A and B)

*Case* 2—E.K. is a 56-year-old woman who began losing central vision at the age of 21 years. The onset of symptoms was gradual and progressed over a period of 10 years, during which time repeated changes of glasses brought only transient and minimal improvement. She denies night blind-

ness, and has had no difficulty with color perception. For the past 15-20 years there has been a moderate, nonprogressive hearing defect. She states that she did not have spontaneous menarche; at the age of 16 years her first menstrual period was "brought on by an injection" (presumably a crude estrogenic compound). These injections were given monthly for a period of about five years, each time resulting in apparently normal menses, but on the few occasions that she did not get these injections, she did not experience bleeding. The development of secondary sex characteristics (i.e., breasts and female hair distribution) did not begin until about 12-18 months after she began receiving the injections, but thereafter development progressed normally. There was no masculinization or defeminization after the injections were stopped. She has not had a single menstrual period since the last injection some 36 years ago.

General physical examination revealed an apparently normal, healthy female. Laboratory studies of the blood and urine were within normal limits. X-ray films of the chest and skull were negative, and the VDRL was nonreactive.

Otologic examination demonstrated a marked neurosensory hearing loss for frequencies over 2000 cps. There were no defects noted in the external auditory apparatus including tympanic membranes.

The central visual acuity was hand movements, both eyes, but she was able to count fingers well at five feet with eccentric viewing. The refractive error was RE: —0.75 sph., LE: —0.50 sph. ⌒ —0.50 cyl. ax. 90. External examination of the adnexa and anterior segments revealed no abnormalities. Ocular motility was normal as was the pupillary response. Applanation tensions were RE: 18 mm Hg, LE: 20 mm Hg. The lens and vitreous were clear in both eyes. There were yellowish, mottled lesions in the macula of both eyes, covering an area of about 2 disk diameters, and no foveal light reflex was seen. The posterior pole had many "bone-corpuscle" pigment deposits with a few rounded pigment spots in the macula areas, but no abnormal pigment was seen anterior to the equator. The vessels were slightly attenuated with sheathing of the arterioles. The disks appeared pale and waxy. (Fig. 2-C and D)

*Case* 3—R.M. is a 48-year-old woman. At the

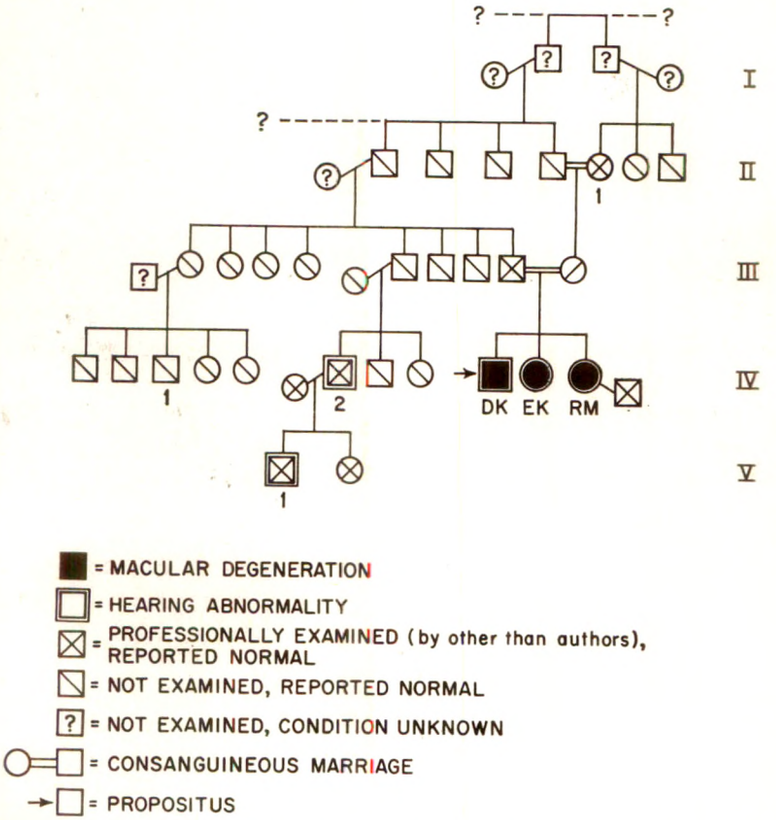



Fig. 1 (Reinstein and Chalfin). Family pedigree. Note the consanguinity of the parents and maternal grandparents of the siblings studied. The endocrine pathology (hypogenitalism) referred to in the text is not indicated in the above figure.

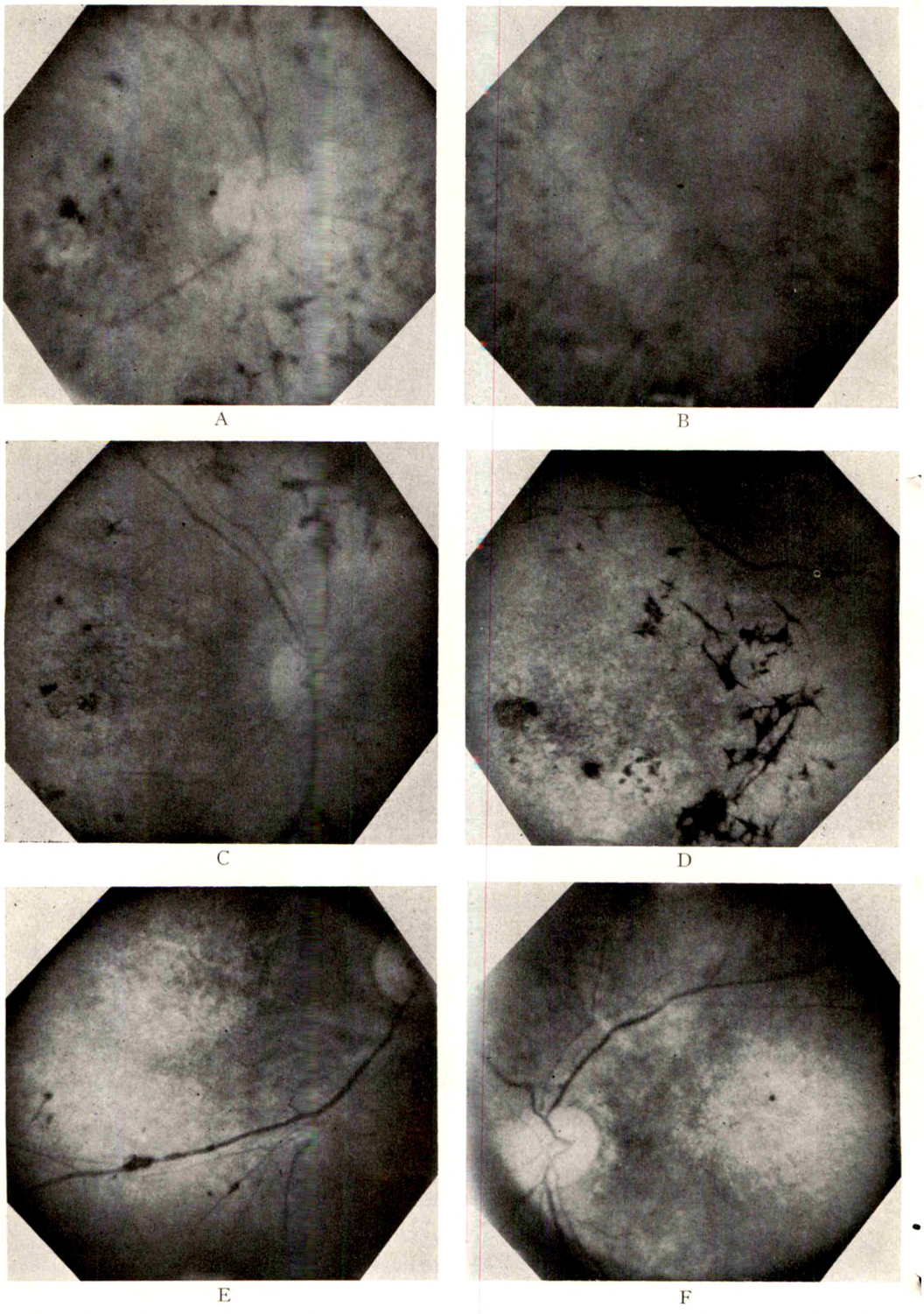



Fig. 2 (Reinstein and Chalfin). Fundus photographs. (A and B) Case 1 (DK). (C and D) Case 2 (EK). (E and F) Case 3 (RM).

age of 15 years, with the onset of the visual disturbance in the second of her two older siblings, she was given a thorough eye examination and states that she was told that her vision was "20/20 in both eyes and there were no abnormalities." (At the same time, both her parents also had their eyes examined, and no abnormalities were reported.) She experienced the onset of central visual loss at about age 32, and noted a rapid deterioration during the next three to five years. Hearing loss was first noted about five years ago. She, too, never had spontaneous menarche and had menses induced at age 16 by an injection. Breast development and growth of pubic hair began one year later and progressed normally thereafter. After five to six years of monthly injections, she elected to stop the treatments, and has not menstruated since. There have been no changes in the secondary sex characteristics since that time.

Physical examination was within normal limits. All laboratory studies, including x-ray examination of the chest and skull, were normal, and the VDRL was nonreactive.

Otologic examination showed moderate neurosensory hearing loss, but the external auditory apparatus was normal.

Central vision was light perception, both eyes, and she was able to count fingers at three feet with eccentric viewing. Retinoscopy showed an error of —0.50 sph. ⊃ —0.75 cyl. ax. 90, both eyes. The adnexa and anterior segments were normal as was the ocular motility. The pupils were equal and reactive. Applanation tensions were 19 and 20 mm Hg, respectively. There was early nuclear sclerosis and trace posterior subcapsular opacities in both lenses, but the vitreous was clear in both eyes. The macular lesions were identical to those seen in her two siblings, and covered an area of 2 disk diameters in each eye. No foveal light reflex was seen. There was practically no abnormal pigment seen, however, and the few deposits noted were confined to fine "lacy" lesions which appeared to encircle the blood vessel walls in the posterior pole. There were two small round pigment spots in the macular area of the right eye. The retina appeared normal anterior to the equator. The vessels were only slightly narrowed, and the sheathing was much less prominent than in her older siblings. Both disks appeared normal (Fig. 2-E and F).

## Special studies

In addition to the findings reported above, each of the three patients underwent the following examinations:

*Color vision*—Due to the marked impairment of vision, the patients were unable to perceive the details of the standard AO-HRR Pseudoisochromatic plates. Color sense was tested instead with 20-mm round test objects from the Berens' Test Object Set. Red, blue green, and white objects were used. The patients were able to identify readily the color of each, but they had to view them eccentrically to do so.

*Visual fields*—Peripheral fields were plotted with the Goldmann perimeter using a 16 $mm^2$ white test object at maximum illumination (Fig. 3). Despite the large, dense central scotoma in all six eyes, fixation was quite steady and the results were reproducible. In five of the six eyes there was a generalized depression of the peripheral field. The right eye of Case 3, however, showed only slight depression for the isopter plotted.

*Dark adaptation*—Simultaneous binocular evaluation of the dark adaptation thresholds were with the Goldmann-Weekers Dark Adaptometer. The patients were unable to maintain steady fixation for the full time of the test. Five minutes of total dark adaptation was followed by light adaptation at 3200 asb for seven minutes, and the thresholds of perception of a striped test field of 100% contrast was measured for 30 minutes. The initial (maximum) luminosity of the ground of the test field was 475 asb. The resulting curves (Fig. 4) show subnormal thresholds and decreased amplitudes.

*Electroretinography*—Photopic and scotopic ERG responses were measured on two of the three subjects (Cases 1 and 2). The photopic responses were made without specific control of the light-adapted state. Immediately after recording the photopic curves, the patients were adapted to total darkness for 10 minutes. For scotopic testing, a red filter was placed in front of the flashing light. In both instances the flicker frequency was 2/second and a total of 75 flashes were given. The photopic electroretinograms show marked depression with the individual wave components just recognizable, while the scotopic tracings are totally extinguished (Fig. 5).

*Audiometry*—Bone and air conduction thresholds were measured with the Beltone Clinical audiometer (Model 15 CX). Stimulus frequencies ranged from 250 to 8000 cps

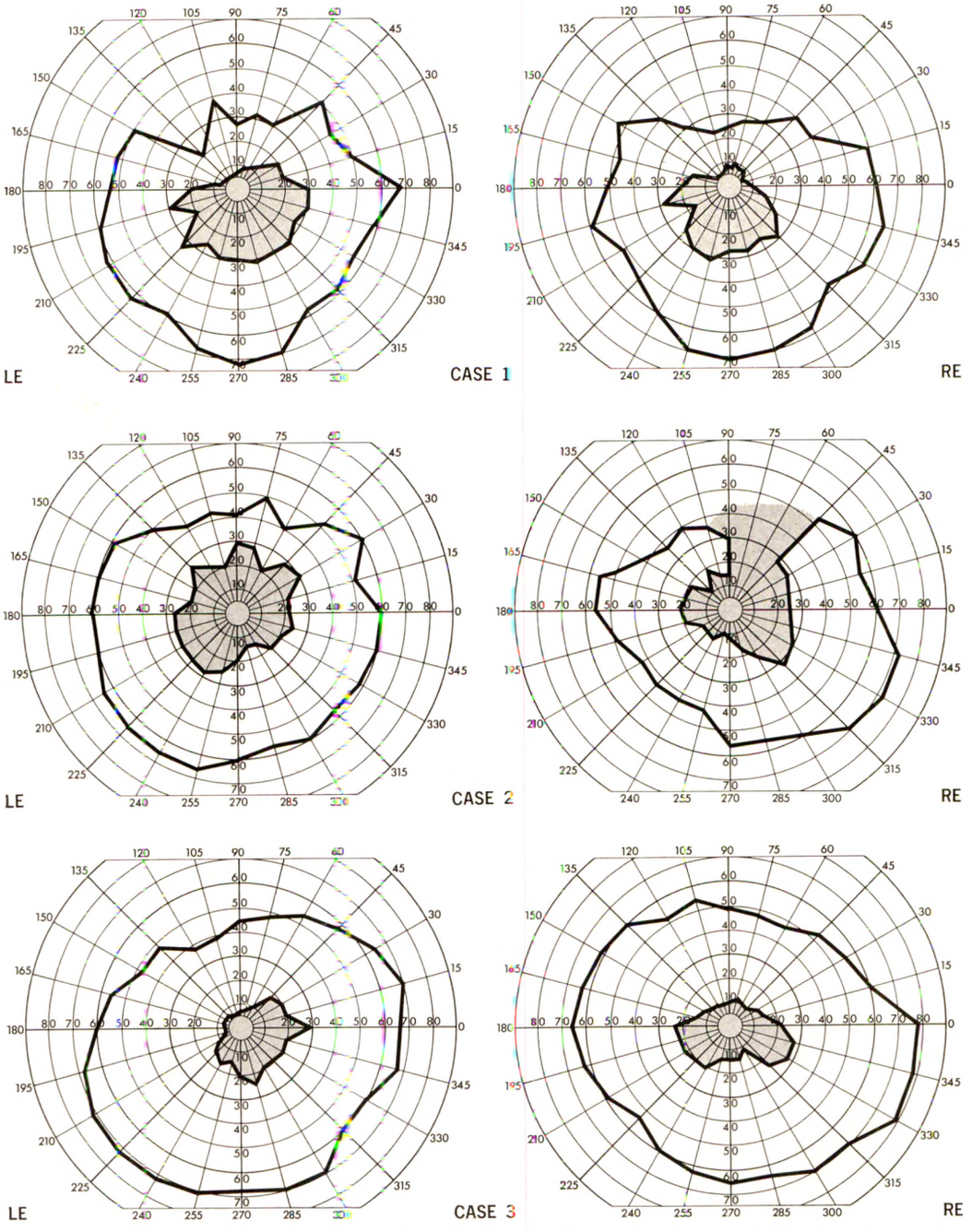



Fig. 3 (Reinstein and Chalfin). Visual fields. The isopter plotted was the same in all six eyes, but the extent of the peripheral depression is greatest in Case 1 and least in Case 3.

(Fig. 6). The findings indicate a neurosensory hearing defect most pronounced in the higher frequency ranges.

*Sense of smell*—Gross testing revealed no signs of anosmia in any of the three patients.

*Chromosomal studies*—Karyotyping was done on samples of heparinized peripheral blood of two of the three patients (Cases 2 and 3) after the method described by Valenti and Vethamany.[2] The karyotypes of the two patients tested in this study were normal with respect to chromosome number (46) and configuration.

## Discussion

Many forms of hereditary retinal dystrophies are described as distinct entities, and numerous classifications have been proposed.[3-7] Though the clinical manifestations vary considerably, several authors postulate a common genetic defect throughout this group.[5,6,8-13] There is lack of agreement, however, on a single uniform classification, or even the basis on which such a classification might rest. Several factors would seem to contribute to this problem: (1) the observed variations in a given form of dystrophy from one pedigree to the next as to pattern of inheritance, age of onset of symptoms, and area and extent of retina involved; (2) the varying association of many of these dystrophies with other ocular and extraocular genetic defects; (3) the occurrence of atypical forms; (4) in long-standing disease, senile vascular changes in the choroid often result in additional secondary changes in the overlying retina, producing a mottled appearance, and this may lead to difficulty in distinguishing one form of dystrophy from another on the basis of the appearance of the fundus. Despite all this, it is common for affected members of a family to parallel one another closely in the clinical manifestations of the disease.

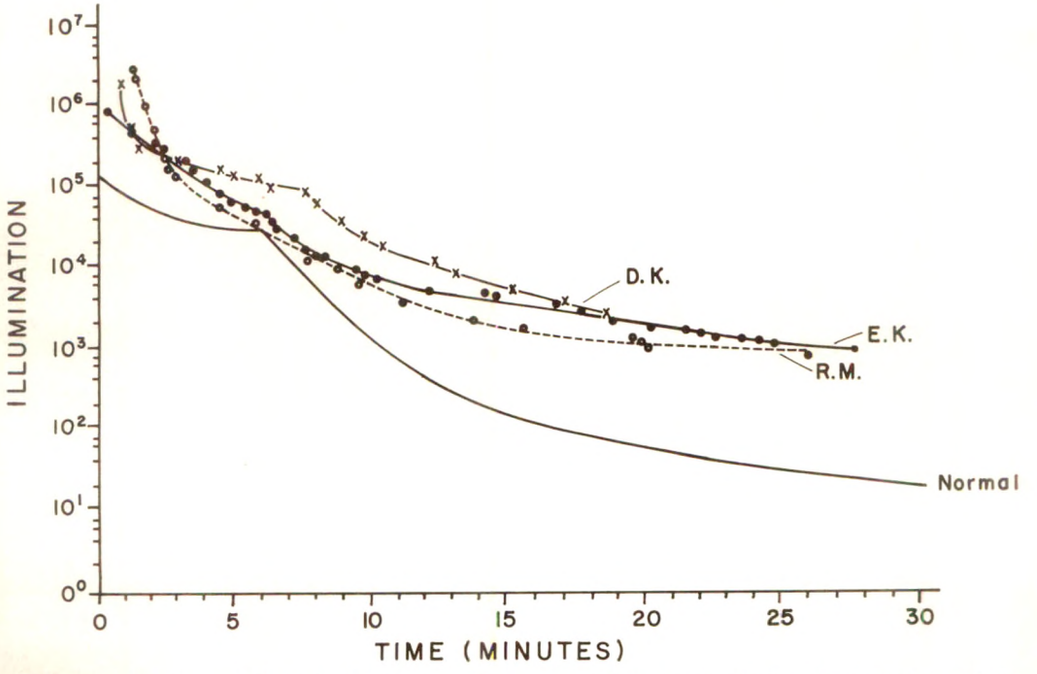



Fig. 4 (Reinstein and Chalfin). Dark adaptation curves. Both the amplitudes of adaptation and the absolute thresholds are subnormal. The configuration of the curves is not characteristic of either pure rod or pure cone dysfunction.

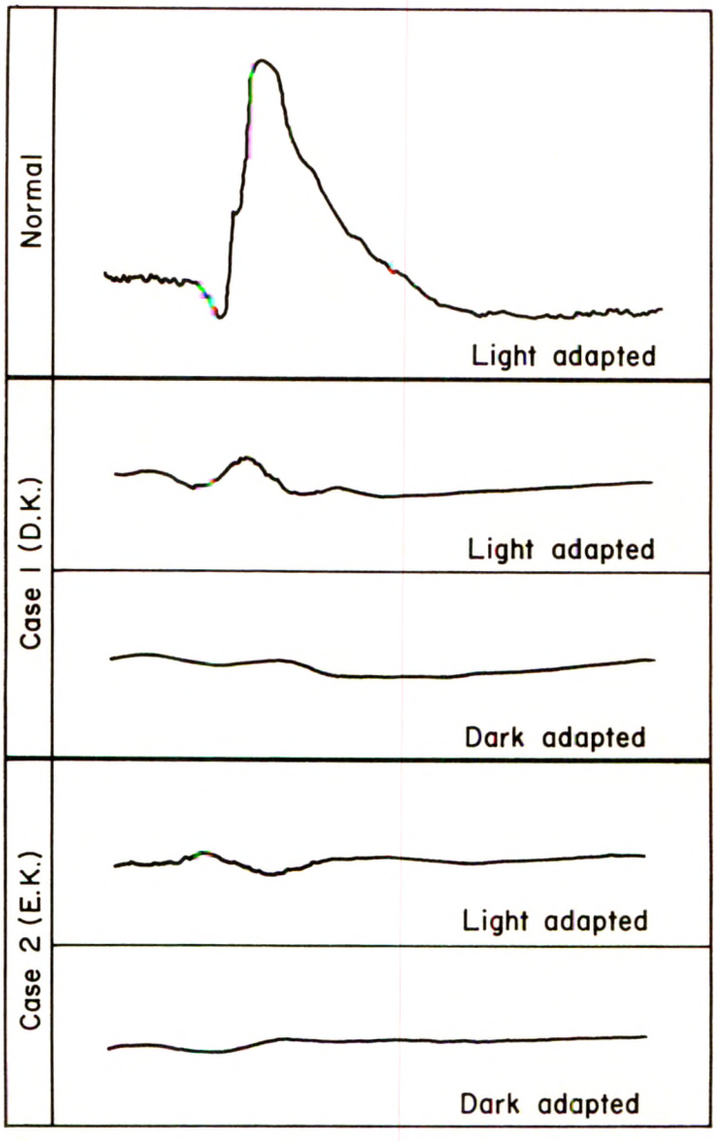



Fig. 5 (Reinstein and Chalfin). Electroretinograms. The photopic curves are markedly depressed while the scotopic curves are completely extinguished.

Numerous pedigrees have been described in which two or more abnormalities occur simultaneously in several individuals, while appearing as isolated disorders in other family members.[8-13] It has been proposed that the phenotypic variations arise from a single pleiotropic gene rather than from two or more separate genes.[8-13] If this were the case, the observed variations might be explained by the varying expressivity of the involved gene, by the presence of "modifying genes" in some individuals, or by modifying environmental factors such as nutrition. This last might play a significant role in the age of onset of symptoms. However, a demonstrable chromosomal defect has not as yet been identified in the hereditary retinal dystrophies, and experimental procedures

such as gene mapping are not readily applied in human genetics. Insofar as consanguinity leads to a greater congregation of recessive genes, the intermarriage of first cousins in two successive generations in our study is a significant factor. Consanguinity is far from uncommon in such pedigrees, but what is unusual in this case is the 100% phenotypic expression of three autosomal recessive traits in all three siblings.

The coincidence of hereditary retinal dystrophies with other disorders in various combinations is well known. The most commonly observed combination is that of retinal disease and deafness, first described by von Graefe in 1858. The reported coincidence of complete or partial hearing loss with abiotrophies of the retina has varied greatly with different observers, but it is not an uncommon finding. This might be explained by the close embrylogic relationship between the retinal neuroepithelium and the epithelium of the organ of Corti.[11]

Hypogenitalism in association with hereditary retinal disorders has been reported in the Laurence-Moon-Biedl syndrome, and, in a single case by Franceschetti and Klein.[12] The male proband in this study has small, soft testes. This might be a sign of hypogenitalism, but there is no proved history of decreased gonadal function, and no signs of feminization. Furthermore, the testicular changes could be due to simple senile atrophy. His two sisters, though phenotypically normal females, give a history of primary amenorrhea and lack of spontaneous development of secondary sex characteristics. These symptoms could be related to a structural or functional derangement of either the pituitary-hypophyseal system or the ovaries. Although primary amenorrhea and genital hypoplasia due to idiopathic hypogonado-

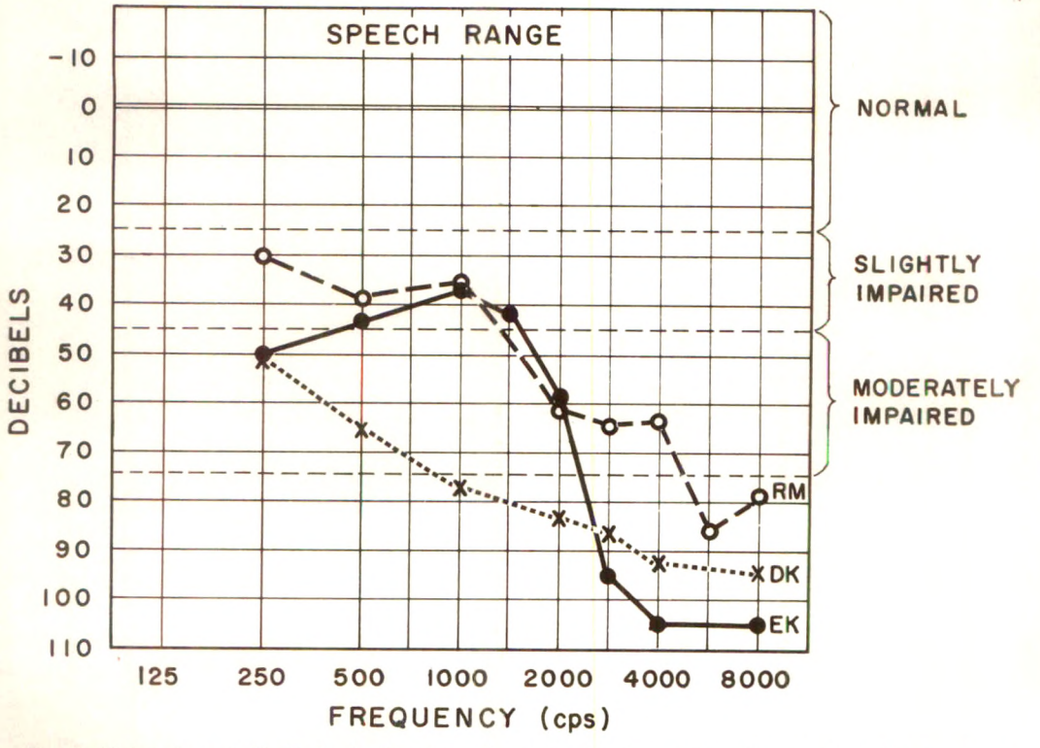



Fig. 6 (Reinstein and Chalfin). Audiometry—air conduction thresholds. The results indicate a neurosensory hearing defect.

trophic hypogonadism is known,[14] it is quite rare, and has not been reported in association with hereditary retinal disorders. The clinical evaluation of ovarian function in these patients was not possible, as they would not consent to laparoscopy with or without ovarian biopsy, and assays of endogenous hormone function would be of questionable validity at their present ages. Therefore, at this time, we cannot isolate with certainty the specific endocrine abnormality; we can only describe the clinical picture and relate it to the possible sites of dysfunction.

The patients in this study manifest an ocular disorder which, on the basis of the appearance of the fundus and the alterations in dark adaptation and electrophysiologic response of the retina, appears to be inverse retinitis pigmentosa. This entity is characterized by a concentration of abnormal pigmentation surrounding the macula and disk, sometimes in the form of a discrete ring, and often with attenuation of the retinal vessels and pallor of the disk. Frequently, a subjacent choroidal sclerosis or atrophy, which may be focal or diffuse also is found.[15] The discrete and prominent macular lesion seen in all six eyes in this study is not a typical finding in central retinitis pigmentosa, but is probably secondary to a choroidal change such as this. This finding led to much confusion in establishing the diagnosis, and serves to illustrate the difficulties in classification alluded to in the opening paragraph of this discussion. In contrast to the "typical" peripheral form of retinitis pigmentosa in which night blindness is the most prominent early symptom, patients with the inverse form lose central vision early, and often prefer dim to bright illumination. Although the dark adaptation curves shown in Figure 4 indicate abnormal function, their configuration is not characteristic for either pure rod or pure cone dysfunction. The three patients denied any subjective night blindness. The finding of unimpaired color vision in all three patients is inconclusive, owing to the gross nature of the testing procedure. However, the marked decrease in central vision precluded the use of more sophisticated studies. The progressive nature of this disorder is illustrated by the increasing depression of the peripheral visual fields (Fig. 3) which corresponds with the duration of symptomatic disease (Case 1, 42 years; Case 2, 35 years; Case 3, 16 years), and which is paralleled by an increasing amount of abnormal pigmentation in the posterior pole (Fig. 2-A through F). It is interesting that while the functional impairment and physiologic alterations seen in Case 3 are almost identical to those seen in her two older siblings, the abnormality in the pigment epithelium supposedly responsible for these changes has produced almost no observable changes in the fundus 16 years after the onset of symptoms.

## Summary

The coincidence of inverse retinitis pigmentosa, deafness, and hypogenitalism was found in three siblings. The patients, a man, age 62 years, and two women, ages 56 and 48 years, all had the onset of progressive visual loss in adult life (ages 20, 21, and 35 years, respectively). They all show typical "bone corpuscle" pigment deposits confined to the posterior pole with discreet mottled macular lesions. Dark adaptation thresholds were elevated, electroretinograms markedly depressed, and the visual fields showed dense central scotomas with peripheral depression. Color vision, however, appeared grossly intact. Audiometry revealed neurosensory hearing defects in all three patients. The two women never had spontaneous menarche and secondary sex characteristics developed only after treatment with exogenous hormones. The man has small, soft, possibly atrophic testes. Study of the family pedigree indicates an autosomal recessive inheritance pattern, but karyotypes revealed no gross chromosomal abnormalities. A review of the literature failed to reveal any previous description of this combination of genetic disorders.

ACKNOWLEDGMENTS

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# AN OCULAR PATHOLOGIC STUDY OF REFSUM'S SYNDROME

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Refsum's syndrome, or "heredoataxia hemeralopica polyneuritiformis,"[7] is thought to be an inborn error of lipid metabolism, with abnormal storage of phytanic acid. The characteristic symptoms are mainly neurologic and the inheritance is autosomal.[1,2] This syndrome was described for the first time by Refsum in 1945 and again in 1949.[3,4] On account of a previous incomplete description of the disease by Thiébaut and associates in 1939,[5] the syndrome is sometimes referred to as Refsum-Thiébaut disease.[6] Since the first reports, 50 observations have been published and about 13 cases have been submitted to postmortem investigation. The eyes were examined in five instances,[7-11] but none of these description of the retinal lesions has included lipid studies.

The purpose of this paper is to present the ocular pathology of a case of Refsum's syndrome and a tentative theory as to the etiology of the associated retinitis pigmentosa characterized in this case by a lipid infiltration of the pigment epithelium.

The characteristic clinical abnormalities of Refsum's syndrome are: atypical retinitis pigmentosa with night blindness and constricted visual fields; pupillary abnormalities, miosis, poor reaction to light and accommodation-convergence; slow and incomplete dilatation following administration of mydriatics and cycloplegics; glaucomatous attacks following administration of a mydriatic; posterior subcapsular cataracts; anosmia; thickened peripheral nerves, chronic polyneuritis; weakness, paresis and amyotrophy of both lower extremities; sensory disturbances and hyporeflexia; ataxia with other cerebellar signs; increased protein in the cerebrospinal fluid without pleocytosis; icthyosis; anomalous development of hands and feet; epiphyseal dysplasia; changes in length of small bones; and cardiopathy.

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## CASE REPORT

The clinical history of this patient was published in 1959.[12] A more detailed report of her general medical history from 1959 until her death, and the autopsy findings will be published elsewhere. The most important clinical and biological findings after her last admission in the Saint-Pierre University Hospital, Brussels, are as follows:

At the age of 44 years, this woman exhibited profound weakness. Her gait was ataxic, and unassisted walking was impossible. There was wasting of the hands, forearms, and legs; absence of abdominal reflexes; and absence of all deep tendon reflexes. She showed generalized icthyosis, loss of cutaneous sensibility, vibratory sense, and stereognosis for the lower limbs. Intention tremor was evident in both upper extremities. There was shortening of the fourth and fifth left metacarpals, and of the fifth right metacarpal, and bilateral shortening of the third and fourth metatarsals. She was both blind and deaf. The right eye showed retinitis pigmentosa with pale yellow disk, surgical aphakia, and total iridectomy. The left eye showed strong miosis, refractory to mydriatics, posterior cataract, and very poor visibility of the fundus. Laboratory test were as follows: total serum lipids, 695 mg/100 ml (phytanic acid, 39%); cerebrospinal fluid protein, 950 mg/100 ml.

*Ocular pathology report*—Both eyes were fixed in 10% Formalin 10 hours after death. The eyes were cut in three fragments from two horizontal sections 5 mm distant from one another. The median fragment of the right eye was embedded in paraffin, that of the left eye in gelatin. The retinal tissues of the four calottes were used for flat preparations after embedding in gelatin and for trypsin digestion. The sections were stained by standard techniques including Nile blue, Sudan III and Sudan black for gelatin-embedded preparations.



Fig. 1 (Toussaint and Danis). Cross-section from the posterior portion of the eye (Sudan III, ×100).

## Discussion

The pathologic abnormalities were identical in the two eyes. The rods and cones were almost entirely missing and the outer nuclear and outer plexiform layers were completely atrophic. The inner nuclear layer was thinned and the ganglion cells were reduced in number. The nerve fiber layer was thickened by glial proliferation. All the retinal vessels were narrowed and some were occluded. The vessels walls were thickened and diffusely loaded with lipid material which appeared red after Sudan III and black after Sudan black staining; in some places they were surrounded with pigmented cells similarly infiltrated with lipid material. On trypsin digestion preparations the atrophic vascular pattern was totally irregular and the walls of numerous main arterial and venous branches showed fibrotic nodular thickenings. In many areas of the posterior pole, the pigment epithelium was absent. Where it was present it was not particularly depigmented and in some areas it appeared deeply pigmented and several layers thick. The pigment epithelium was present from the equator to the ciliary processes. The pigment epithelium of the posterior (Figs. 1 and 2), equatorial (Fig. 3), and peripheral fundus, as well as that of the ciliary processes (Fig.

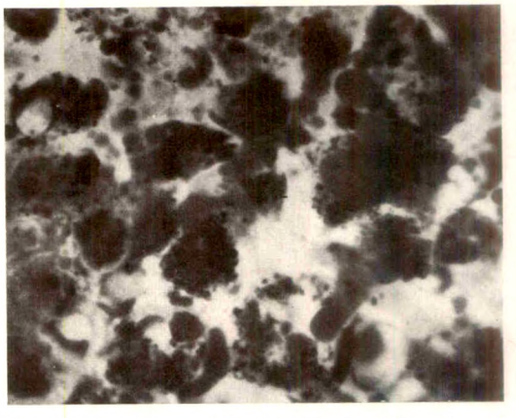


Fig. 2 (Toussaint and Danis). Horizontal section of the pigment epithelium (Sudan III, ×500).



Fig. 3 (Toussaint and Danis). Cross-section from the equatorial region (Sudan III, ×30).

4), was uniformly loaded with lipid material. Lipids were also grossly present in the scleral tissues and in the trabecular tissues surrounding Schlemm's canal (Fig. 5). Sudan III and Sudan black produced similar staining in the cornea and in the pigment epithelium. By contrast, Nile blue stained the pigment epithelium lipids partly blue and partly red (Fig. 6), whereas the lipids stored around Schlemm's canal stained uniformly red. The pigment epithelium of the iris was normal, but the sphincter and dilator muscles were infiltrated with lipids. Bruch's membrane, lamina vitrea, and choriocapillaris were entirely normal. Choroidal vessels did not show sclerosis. Optic nerves showed mild demyelination, but not gliosis. The nerve fibers were normal and the septa showed only mild sclerosis and thickening.

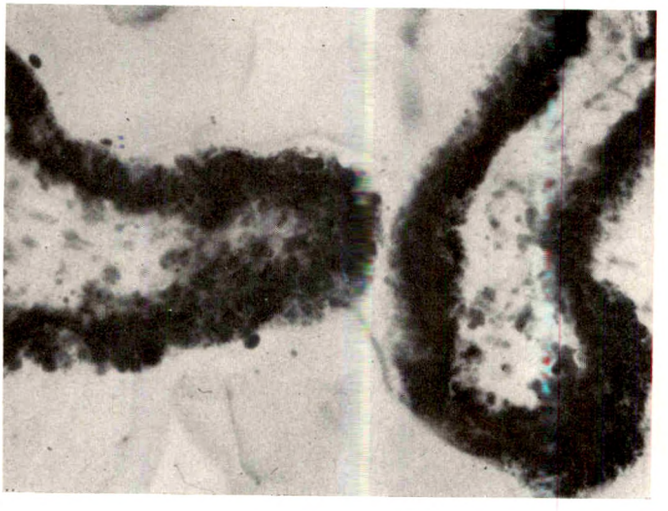


Fig. 4 (Toussaint and Danis). Ciliary processes (Sudan III, ×100).

## Comment

Refsum' syndrome results fron an inborn error of metabolism that induces lipidosis,[13-15] with general metabolic significance. The storage product is phytanic acid (3,7,15-tetramethyl hexadecanoic acid), an abnormal branched-chain fatty acid[2,13-19] found in the serum and in many different cell types. Little is known about the catabolism of phytanic acid in normal persons or in Refsum's disease. The relationship between accumulated phytanic acid and the clinical manifestations of Refsum's syndrome is still not clear. Histologic studies suggest that the peripheral neuropathy may be due to mechanical effects of the accumulated lipids, but this purely mechanical explanation does not satisfactorily explain the other symptoms (e.g., cataracts, retinitis pigmentosa, skin changes, heart disease). Animals fed with phytol or phytanic acid show an accumulation of phytanic acid without any pathologic changes in the retina or in the peripheral and central nervous system such as those observed in Refsum's syndrome.[20,21] Moreover, the demonstration of phytanic acid in two healthy mothers of patients with Refsum's disease also does not support a relationship between phytanic acid and clinical symptoms.[14]

The esterification of vitamin A has been found normal in liver tissue of patients with Refsum's disease[22] and must therefore be presumed to be normal in the pigment epithelium of the eye. One is left with the hypothesis that the massive accumulation of

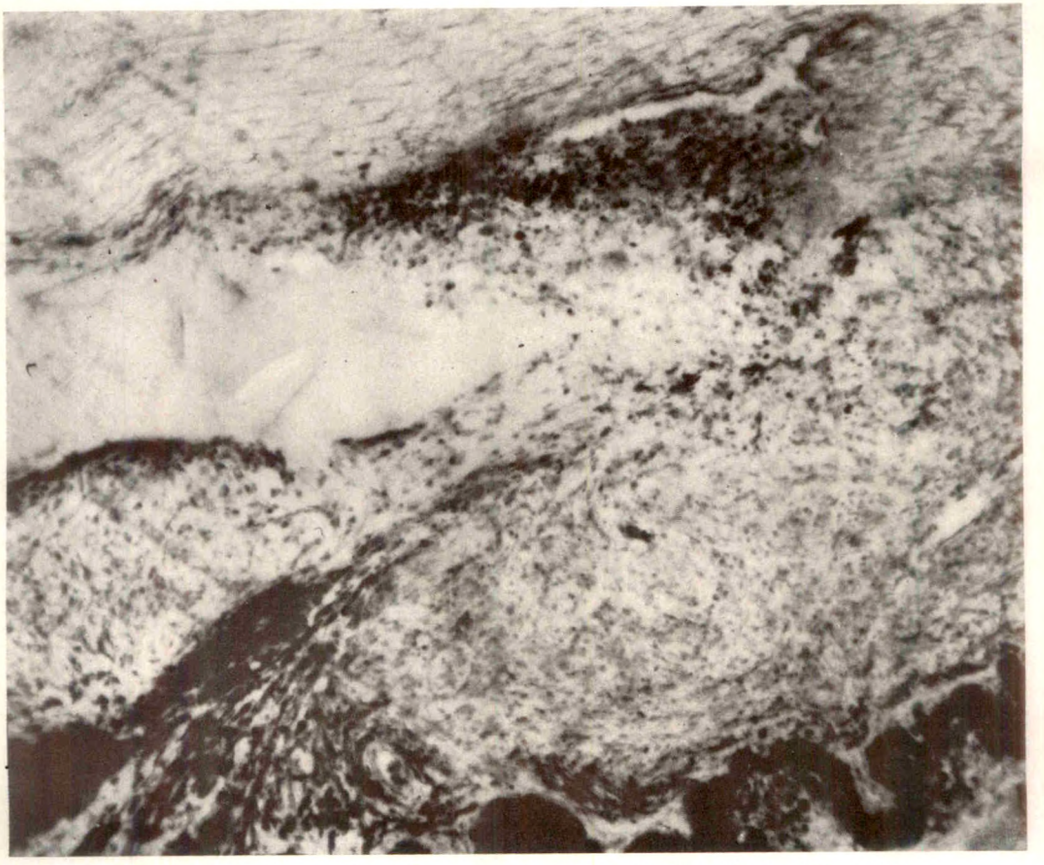


Fig. 5 (Toussaint and Danis). Angle of anterior chamber (Sudan III, ×100).

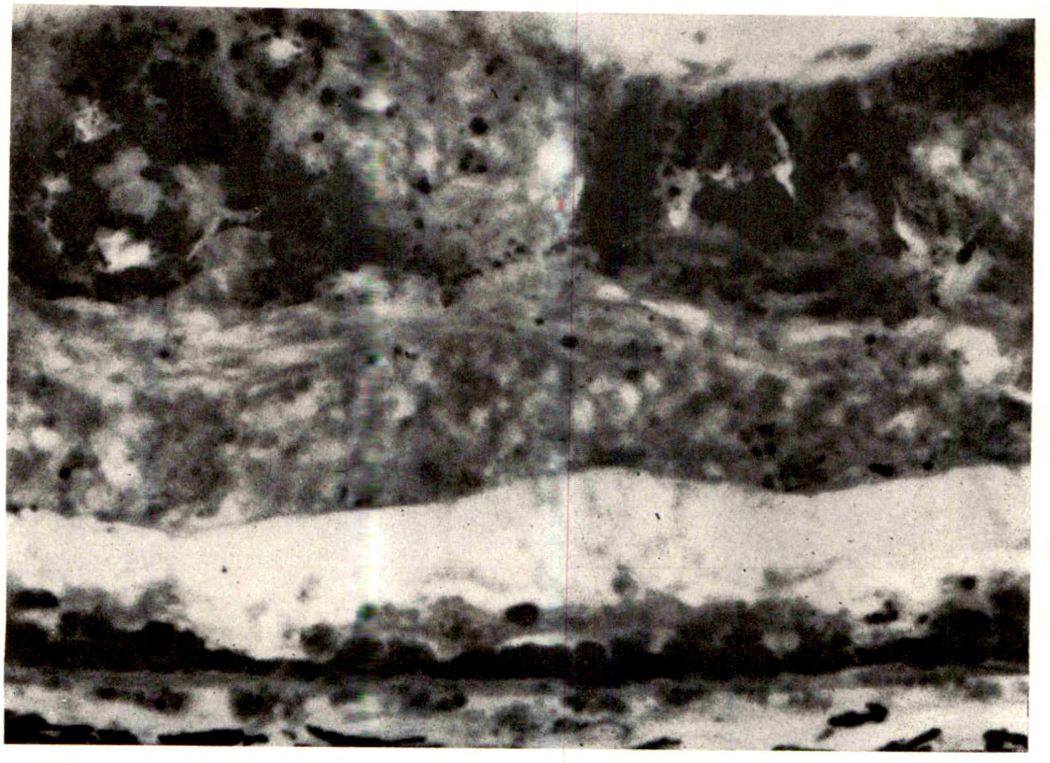


Fig. 6 (Toussaint and Danis). Cross-section from posterior portion of eye (Nile blue, ×100).

lipid in the epithelium, as shown in the present sections, interferes in some way with the transfer of retinal to the photoreceptors. No such accumulation of lipid has been found in a case of idopathic retinitis pigmentosa unassociated with Refsum's disease.[22]

The lipid material observed about Schlemm's canal suggests that the glaucoma in Refsum's syndrome following attempts to dilate the pupils results from the release of lipid from the ciliary processes and accumulation in the corneoscleral trabeculae. The reported "aqueous flare" with Refsum's syndrome[23] may have a similar origin.

## Summary

The ocular histopathologic abnormalities are reviewed in a 44-year-old woman with Refsum's syndrome who was blind and deaf and had polyneuritis, cataracts, and retinitis pigmentosa. The most noteworthy abnormality in the ocular tissues was the presence of sudanophilic material in the sclera, trabecular meshwork, iris muscles, and most especially, a coating of the retinal pigment epithelium with fat. It is suggested that this accumulation of lipid interfered with the normal generation of retinal, resulting in degeneration of the photoreceptors.

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# THE ASSOCIATION OF PALE-CENTERED RETINAL HEMORRHAGES WITH INTRACRANIAL BLEEDING IN INFANCY

## A Report of Two Cases

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Hemorrhages into the eye are a common sign of intracranial bleeding. Such hemorrhages may be in the retina, in front of the retina (preretinal or subhyaloid), or in the vitreous. Unusual hemorrhages—hemorrhages with pale centers—were found in the fundi of two children recently treated for intracranial bleeding.

Pale-centered retinal hemorrhages usually indicate either a severe hematologic disorder or septicemia. The association of pale-centered retinal hemorrhages and intracranial bleeding has not been previously described.

### Case reports

*Case* 1—This infant was admitted to University Hospitals on August 1, 1968, at the age of 31 days. Her mother had had a normal pregnancy, although the delivery had been by cesarean section because of a previous cesarean section for cephalopelvic disproportion. The baby's birth weight was 2640 g. She had progressed as a normal infant until two days before admission, when she became irritable without obvious cause; she had not been injured or exposed to infections. The day after onset of irritability, she did not eat and seemed feverish. Intermittent spells, during which she drew up her knees, shook her arms, and grew rigid, became increasingly frequent.

Examination on admission revealed the infant to be a normally developed white girl, weighing 3070 g. Her heart rate was 170/minute, and her temperature was 35.6° C. Seizures occurred every 10 to 15 minutes and lasted about one minute. During these, she would stiffen, develop rhythmic eye movements, and utter short cries. Between seizures she was unresponsive. Her anterior fontanel was tense. There were no skin lesions or enlarged lymph nodes. The spleen was not enlarged, but the liver extended 4 cm below the right costal margin. No bruises or other marks of trauma were seen. In the left fundus there were numerous retinal, preretinal, and vitreous hemorrhages. The right fundus was normal. Grossly bloody cerebrospinal fluid was obtained from a lumbar puncture. The baby was treated with ampicillin and paraldehyde.

The following day she had numerous pale-centered hemorrhages in the previously normal right retina (Fig. 1). In the left eye, the entire retina was hemorrhagic; where separate hemorrhages could be distinguished, they, too, had pale centers. A tap of the left cerebral ventricle produced clotting blood. Treatment was changed to kanamycin and diphenylhydantoin.

Laboratory studies showed a hemoglobin of 7.8 g%, packed cell volume of 25%, white blood count of 19,300/mm$^3$, and a platelet count of 790,000. Her differential white blood count showed 7% metamyelocytes, 9% band forms, 48% segmented polymorphonucleocytes, 33% lymphocytes, and 3% monocytes. Urine, BUN, creatinine, sugar, carbon dioxide combining power, chloride, sodium, potassium, and calcium levels were normal. Cultures of blood and spinal fluid were negative. Skull and chest x-ray films were normal.

Seizures became more frequent and could not be controlled by sedatives. On the third hospital day the child died. The final diagnosis was intraventricular cerebral hemorrhage. Her parents did not allow an autopsy.

*Case* 2—This seven-month-old black girl was healthy until December 14, 1968, when she fell from a bed, striking her head so severely that she was

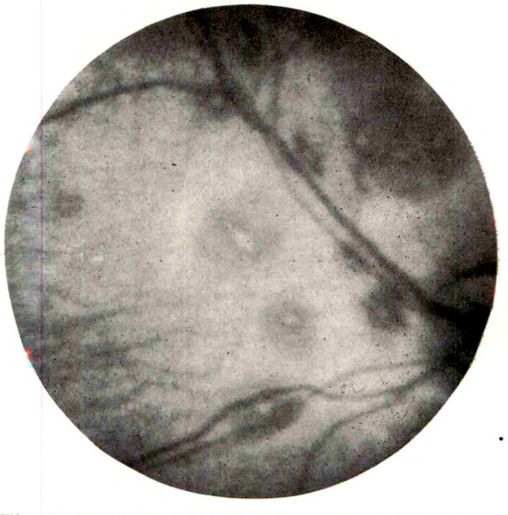


Fig. 1 (Phelps). Right fundus, Case 1. Numerous intraretinal hemorrhages with pale centers.

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unconscious for a brief time. She was hospitalized in her home town; there she began to vomit and became lethargic. When aroused she was irritable. Two days following her injury, she developed seizures and was transferred to University Hospitals. Examination showed a lethargic infant with a heart rate of 84/minute, a temperature of 37.2°C, and a respiratory rate of 30/minute. She was having periodic left-sided seizures with a left hemiparesis between seizures. There were numerous white-centered intraretinal hemorrhages and large preretinal hemorrhages in both fundi (Fig. 2).

Subdural taps yielded 6 ml of blood-tinged xanthochromic fluid from the right side and 4 ml of similar fluid from the left. She was treated with phenobarbital.

Laboratory tests included: hemoglobin of 10.9 g%, packed cell volume of 32%, white blood count of 9,400/mm$^3$, and a differential count of 62% segmented polymorphonucleocytes, 1% eosinophils, 28% lymphocytes, and 9% monocytes, with normal cellular morphology. BUN, creatinine, carbon dioxide combining power, chloride, sodium, potassium, calcium, phosphorus, and sugar were all present in normal amounts in the child's blood. Cultures of blood and spinal fluid were negative. X-ray films of her chest and skull were normal. An electroencephalogram taken on the third hospital day was normal.

Subdural taps repeated on the third and fifth hospital days produced little fluid. By the sixth day she seemed completely recovered, and two days later she was discharged. On the day of discharge, there were only scattered remnants of the once numerous retinal hemorrhages.

The final diagnosis was bilateral subdural hematomas.

## Discussion

Retinal hemorrhages occur in about 20% of adults who have subarachnoid bleeding,[1] but are rare in adults who have subdural hematomas. In contrast, infants frequently have retinal hemorrhages in association with either type of intracranial bleeding.[2]

The generally accepted theory for the production of retinal hemorrhages by intracranial bleeding is that of Ballentyne.[3] Blood leaking from an intracranial vessel enters a non-distensible space. This causes the intracranial pressure to rise abruptly to a level approaching that of the arterial blood pressure. The cavernous sinus, into which most of the orbital venous blood drains via the ophthalmic veins, shares in the high intracranial pressure. Flow through the ophthalmic veins ceases until there is a buildup of pressure transmitted from the ophthalmic artery.

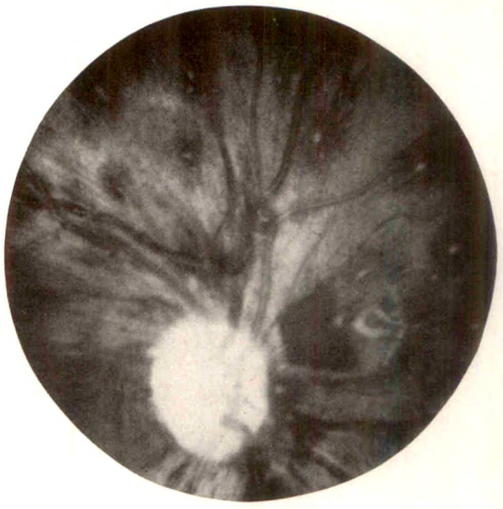


Fig. 2 (Phelps). Right fundus, Case 2. Peripapillary edema, one preretinal hemorrhage, and many intraretinal hemorrhages with pale centers.

An intolerable transmural orbital venous pressure is the result, and the vessel walls rupture at their weakest points. The frequent occurrence of small hemorrhages elsewhere in the orbit is evidence for this theory.

The unusual feature in these two infants is the pale centers of the retinal hemorrhages. Pale-centered retinal hemorrhages should alert a physician to search for chronic sepsis or for hematologic disorders such as leukemia, aplastic anemia, iron deficiency anemia, or pernicious anemia.[4,5] They are also rarely encountered in scurvy, diabetes, and collagen vascular disorders.[6,7]

It is appropriate, because of the widespread misuse of the term, to note that Roth's spots are not white-centered hemorrhages. Roth, a pathologist, described the gross and microscopic appearance of retinal hemorrhages and white, non-hemorrhagic retinal lesions in the eyes of patients who had died from acute septicemia.[8,9] The hemorrhages did not have white centers. The white lesions were composed of swollen nerve fibers, often containing a sharply circumscribed shiny swelling resembling a nucleus. In today's terminology, it seems likely that Roth was describing cotton-wool

patches which histologically were a collection of cytoid bodies.

Litten[10] first described the ophthalmoscopic picture of white-centered hemorrhages in the retinas of septic and anemic patients. He also described white spots without hemorrhages, which he properly called "Roth'sche Flecken." Unfortunately, subsequent writers misapplied the eponym "Roth" to the pale-centered hemorrhages which Litten first described. (It is an interesting coincidence that Litten is also credited with the first ophthalmoscopic description of a patient with retinal hemorrhages occurring in association with intracranial bleeding.[11])

In the two infants described in this report, the pale-centered retinal hemorrhages led to a fruitless search for septicemia and blood cell disorders. In each case the clinical findings and negative blood cultures made septicemia unlikely. The first infant had moderate anemia, a mild leukocytosis with some immature forms in the granulocytes, and a moderate thrombocytosis. It might be argued that she had leukemia; however, it was our interpretation that the high white cell and platelet counts were a secondary response to her severe intracranial bleeding. The second infant had normal blood counts.

What might cause the centers of these hemorrhages to be pale? Little is known about the white centers of retinal hemorrhages in any of the several conditions wherein they occur. Focal accumulations of leukocytes have been found in some pale-centered hemorrhages of leukemia,[12] bacterial endocarditis,[13-15] and pernicious anemia.[5] Those of aplastic anemia and aleukemic leukemia have not yet been examined histologically.[5] Leinfelder[10] has proposed four possible mechanisms for a white center in a retinal hemorrhage: a nest of leukocytes, a group of cytoid bodies, a collection of serum, or a central clearing of a previously homogenous hemorrhage. If the retinal hemorrhages in the two cases described here were produced by a sudden increase in venous pressure, according to the theory of Ballentyne,[3] it is difficult to imagine how any of these four mechanisms would occur.

## Summary

Pale-centered retinal hemorrhages were found in the eyes of two children with intracranial bleeding. Neither child had septicemia or a blood dyscrasia, the usual causes of pale-centered retinal hemorrhages. Although retinal hemorrhages commonly accompany intracranial bleeding, pale centers of the hemorrhages have not been previously described. The pathogenesis of the pale centers is unknown.

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# RHEGMATOGENOUS RETINAL DETACHMENT AND CHOROIDAL MELANOMA

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This report describes an eye with retinal breaks and a retinal detachment containing two separate malignant melanomas.

## CASE REPORT

A 62-year-old white woman was referred to the Bascom Palmer Eye Institute because of recent findings of a retinal detachment in association with a probable tumor of her right eye. The patient gave a history of progressively decreasing visual acuity for two years. The past history, including a systems review, was otherwise normal. Examination revealed vision of 20/400 in the right eye and 20/20 in the left eye; a superior field defect to finger counting was present on the right. The right pupil reacted normally to consensual light but incompletely to direct light. Extraocular movements and slit-lamp examination of the anterior segments were normal. Applanation tensions were 20 mm Hg in each eye. Pigment particles were scattered throughout the vitreous in the right eye. Fundus examination showed a near total retinal detachment in the right eye and a large horseshoe tear within the area of detachment superotemporally (Fig. 1). In addition, there was a round retinal break with an overlying operculum superotemporally in an area of attached retina. A large solid-appearing mass extended inferiorly from the posterior pole toward the ora serrata. Though seen indistinctly, its surface appeared to be smooth and mottled with pigment. A defect to transillumination was present. The clinical diagnosis was malignant melanoma of the choroid, retinal detachment, and retinal breaks. Enucleation was advised and performed.

Grossly, the eye was normal. On cross section, the retina was almost totally detached and contained two breaks, superotemporally. A 10 by 10 mm elevated gray-brown mass involving the choroid was visible inferiorly under the detached retina. A pigmented plaque-like choroidal lesion that was distinctly separate from the main lesion was situated temporally in the region of the ora serrata, with extension into the posterior half of the pars plana of the ciliary body.

Microscopically, the anterior segment was normal. A large choroidal tumor near the disk extended inferiorly to the ora serrata. Its cells were predominantly of medium size with oval vesicular nuclei, prominent nucleoli, and scanty eosinophilic cytoplasm arranged in places in dense whorls. Many epithelioid cells with irregular nuclei and abundant cytoplasm were also present (Fig. 2). A moderate amount of pigmentation was irregularly distributed within the tumor. Bruch's membrane was intact over the tumor. Tumor cells extended along the intrascleral vascular channels beneath the mass. A vortex vein extending outside the eye contained an intraluminal mass of tumor cells.

The smaller temporal tumor contained small, relatively uniform cells with hyperchromatic nuclei and scanty cytoplasm and larger fusiform cells with elongated vesicular nuclei. Nucleoli and nuclear chromatin bars were present in variable distributions. Scanty pigmentation was present in the posterior half of the tumor, but the more anterior and internal regions were heavily pigmented. Detachment of the retinal pigment epithelium demonstrated hyperplasia and irregularity in this area. Large drusen were present in Bruch's membrane in the same region. The choriocapillaris was absent in some areas, whereas in others it appeared normal (Fig. 3 and 4).

The retina was detached over both tumors and elsewhere. Superotemporal sections showed a retinal horseshoe tear with vitreous attached to the anterior flap (Fig. 5).

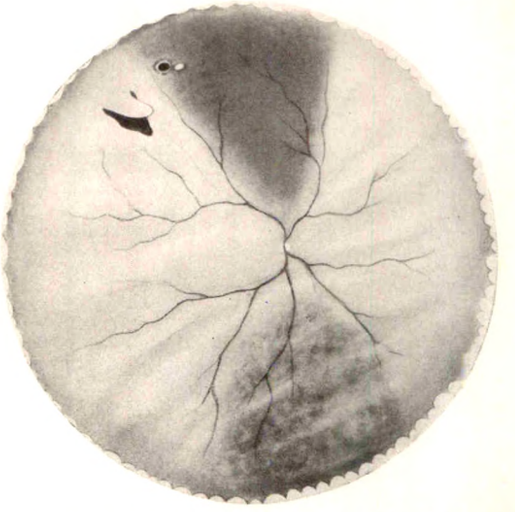


Fig. 1 (Robertson and Curtin). Drawing of fundus showing large choroidal melanoma partially camouflaged deep to a retinal detachment. A horseshoe tear is located superotemporally in area of detached retina and a round hole with operculum can be seen in the sector of attached retina.

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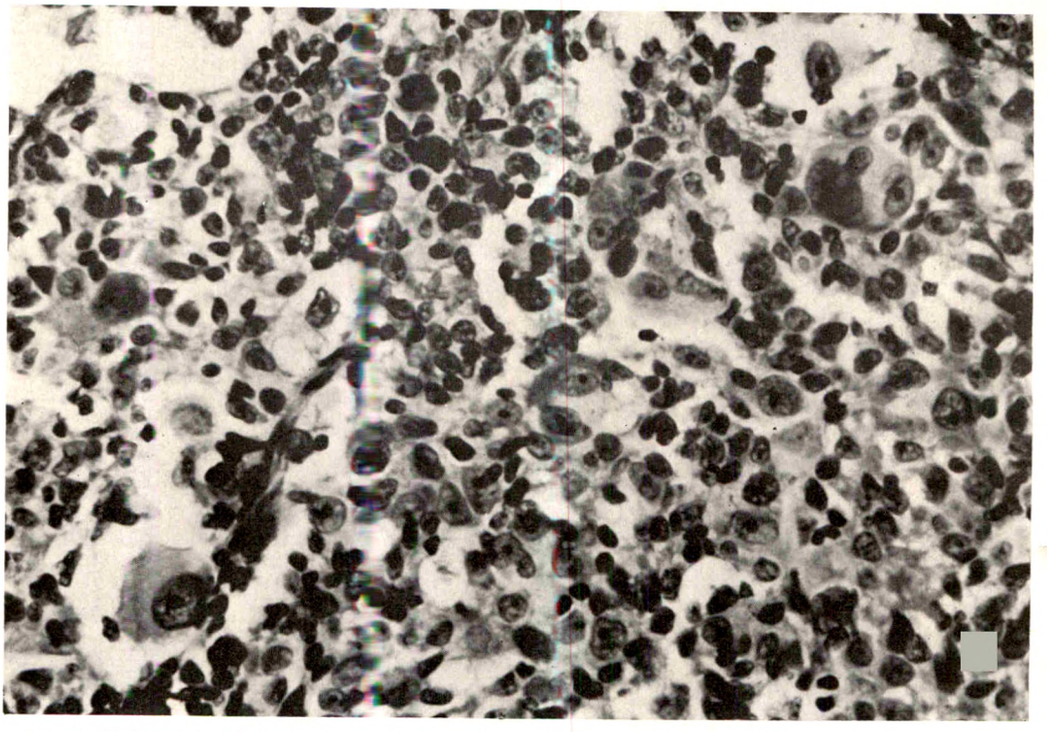


Fig. 2 (Robertson and Curtin). Larger tumor has epithelioid and spindle cells (hematoxylin and eosin, ×440).

Pathologic diagnoses were malignant melanoma of the choroid, mixed type; malignant melanoma of the choroid and ciliary body, spindle cell type; retinal detachment; and retinal horseshoe tear.

## Comment

The association of malignant tumors of the choroid and retinal breaks with or without retinal detachment only recently has been documented in literature. Although several articles have reported this relationship,[1-3] only four cases have been reported which include the histopathology of both the tumor and the retinal break.[3-6] Boniuk and Zimmerman[3] reported a case of choroidal melanoma in which an incidental retinal break was discovered histologically. Manschot[4] re-

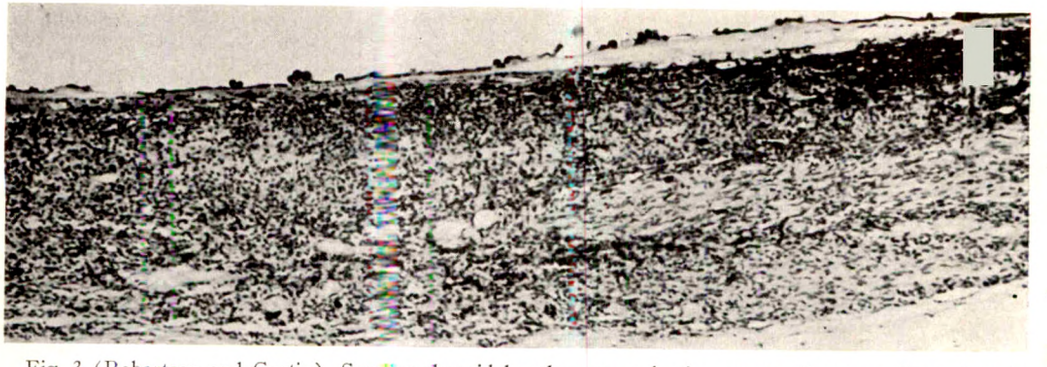


Fig. 3 (Robertson and Curtin). Smaller choroidal melanoma under low power (hematoxylin and eosin, ×70).

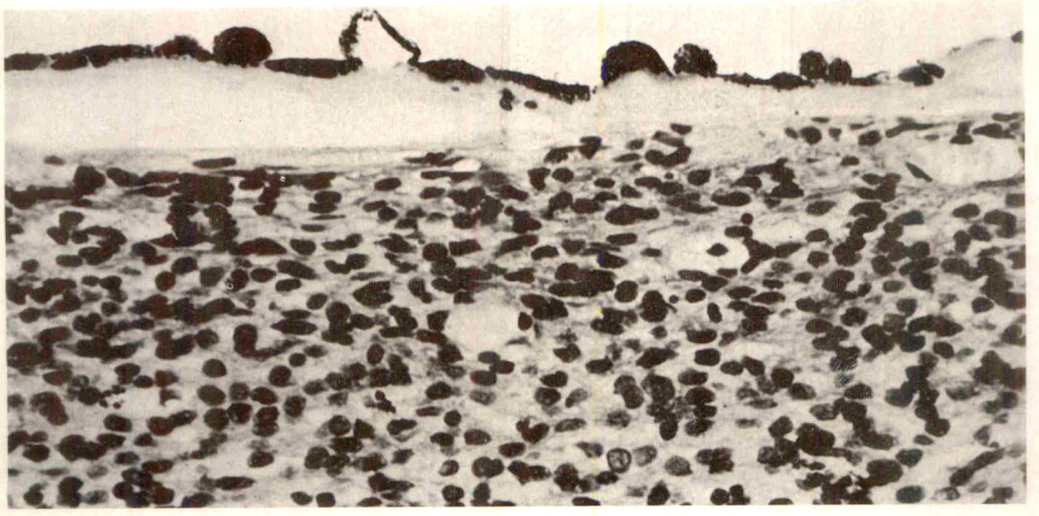


Fig. 4 (Robertson and Curtin). Same lesion as in Figure 3, showing variable cellular morphology, irregular pigment deposition, and area where choriocapillaris is absent (hematoxylin and eosin, ×440).

ported a case in which a hole overlying a melanoma in the histologic specimen was believed to have evolved from a degenerated retinal cyst. In the case reported by Berson and associates,[5] a round retinal break was found in the superotemporal quadrant within the detached retina remote from a clinically recognized malignant melanoma. Howard[6] reported a case in which a choroidal metastatic lesion from an adenocarcinoma of the colon was associated with a retinal detachment and a small "fish-mouth" tear.

In the cases reported by Berson's group and by Howard, the retinal detachments might be explained on the basis of the observed hole. In the case reported by Berson and associates, the tumor was recognized and the eye was removed. In the case reported by Howard (the only one with a horseshoe tear), the tumor was not recognized until after unsuccessful retinal detachment surgery was performed. In the present case, a horseshoe tear in the detached retina superotemporally could easily have explained the retinal detachment.

Because 5 to 8% of eyes contain retinal breaks,[7,8] these circumstances of retinal breaks, a retinal detachment, and intraocular tumor will occur by coincidence in rare instances. What are the best ways of avoiding errors in diagnosis? First, the characteristics of the detachment itself should be carefully evaluated. Does the location of the retinal breaks satisfactorily explain the geography of the detachment? Does subretinal fluid readily shift when the patient's head is changed from the vertical to the horizontal position? If the answer to the first question is "no" and the answer to the second is "yes," the ophthalmologist should be particularly alert that the problem is other than a rhegmatogenous retinal detachment. Second, the part of the eye that is behind the detached retina must be appraised. Indirect ophthalmoscopy greatly facilitates the examination because its greater illumination (when compared with direct ophthalmoscopy) gives the examiner a clearer view beneath detached retina. Consequently, an underlying mass is less likely to be camouflaged and overlooked. Third, any area that looks suspicious should be transilluminated. This can be most simply accomplished with the aid of a Finnoff head and an indirect ophthalmoscope. Similar to the scleral depressor, the illuminated Finnoff head is placed behind the region of the eye to

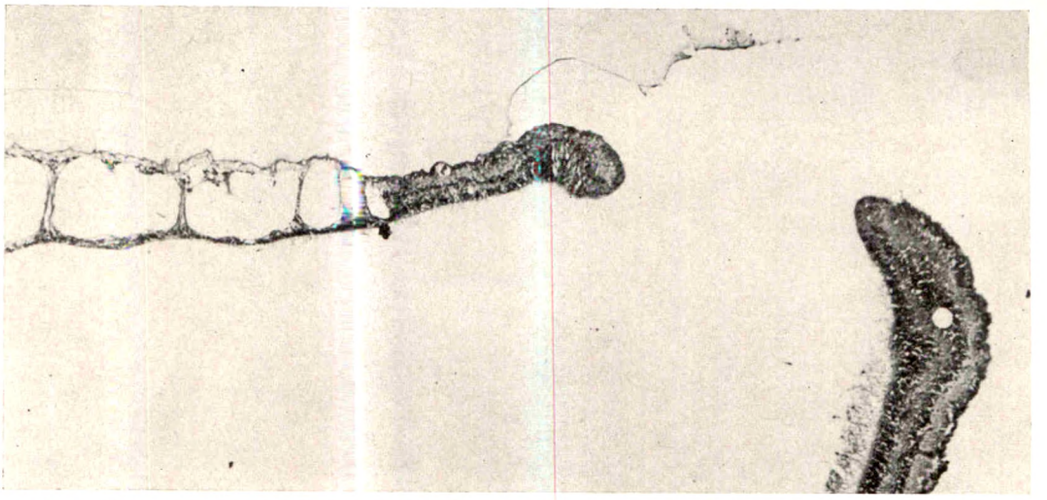


Fig. 5 (Robertson and Curtin). Horseshoe tear showing vitreous attachment to anterior flap (hematoxylin and eosin, ×44).

be studied, while the examiner views this region through the optics of the nonilluminated indirect ophthalmoscope. A mass such as a choroidal melanoma will likely be revealed by a transillumination defect that appears dark against the surrounding illuminated tissue. Hopefully, these considerations will help the ophthalmologist avoid operating for detached retina in the presence of an underlying tumor and thus obviate the complications that have been described by Boniuk and Zimmerman.[3] In our case, the limits of the detachment could have been easily explained by the superotemporal horseshoe tear. Though shifting fluid was somewhat exaggerated, detachment surgery would likely have been recommended had the tumor not been recognized by indirect ophthalmoscopy and further defined by retroillumination in the manner described.

An additional and unusual finding was the discovery on gross pathologic examination of a second small malignant melanoma in the eye of our patient. This tumor was well circumscribed and distinctly remote from the larger tumor. Because of its small size and its cellular structure, the lesion appears to have been relatively inactive. Nevertheless, the cellular characteristics and the changes in the choriocapillaris and pigment epithelium justify classification of this lesion as a malignant melanoma which developed from a separate focus. In referring to multiple origins of melanomas, Reese[9] stated that any malignant melanoma might be accompanied by benign melanomas elsewhere, but he questioned whether two malignant melanomas had ever developed separately in the same eye. Kurz,[10] however, reported a case in which two melanomas arose independently 180 degrees apart in the ciliary body and iris. The present report serves to demonstrate that malignant melanomas also may arise from separate foci within the posterior uveal tract.

## Summary

A case is reported in which the patient's eye contained a rhegmatogenous retinal detachment and two apparently separate choroidal melanomas. Though the geography of the detachment could have been easily explained by the superotemporal horseshoe tear, clinical recognition of one of the tumors underlying the elevated retina led to the correct diagnosis and enucleation. Photomicrographs of the specimen show sections through both tumors and the horseshoe tear.

ACKNOWLEDGMENTS

We thank G. Brock Magruder, M.D., and Stuart N. Willner, M.D., for their referral and treatment of this patient.

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OPHTHALMIC MINIATURE

When ordinary people were told by the dogmatic propagandists of Charles Darwin's theory of evolution that so complex a thing as an eye had come into existence by some vague force known as natural selection, acting on chance minor structural variations, their credulity was taxed to the utmost. Their faith would probably have failed them completely had they been asked to believe that this random and mechanistic process had produced the vertebrate eye and the invertebrate eye in complete independence and more than that, had permitted the invertebrates to originate at least three different kinds of eyes in independence, within the limits of their own phylum.

F. Wood Jones, F.R.S.
*Trends of Life*
London, Edward Arnold & Co., 1953

# EXPERIMENTAL RETINAL DETACHMENT IN THE OWL MONKEY

## VIII. Photoreceptor Protein Renewal in Early Retinal Reattachment

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It has been demonstrated that the degeneration of photoreceptor outer segments, the alterations of the pigment epithelium, and the extinction of the electroretinogram (ERG) produced by experimental retinal detachment can be quickly reversed by surgical reattachment of the retina.[1-4] In addition, autoradiography has demonstrated that the normal renewal of outer-segment protein is changed by experimental retinal detachment.[3] This report describes the effect of reattachment of the retina on the protein renewal of photoreceptor cell inner and outer segments.

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### Materials and Methods

In a series of three owl monkeys (Aotus trivirgatus), each weighing between 600–800 g, retinas were experimentally detached,[6] allowed to remain detached for four weeks, and then were surgically reattached, using a

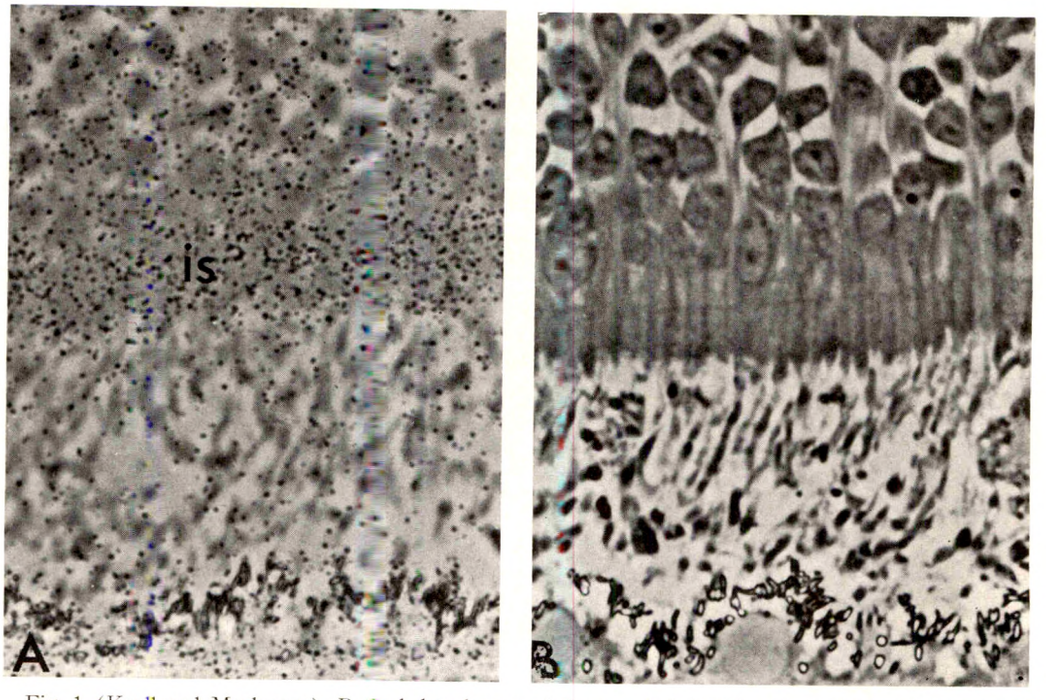
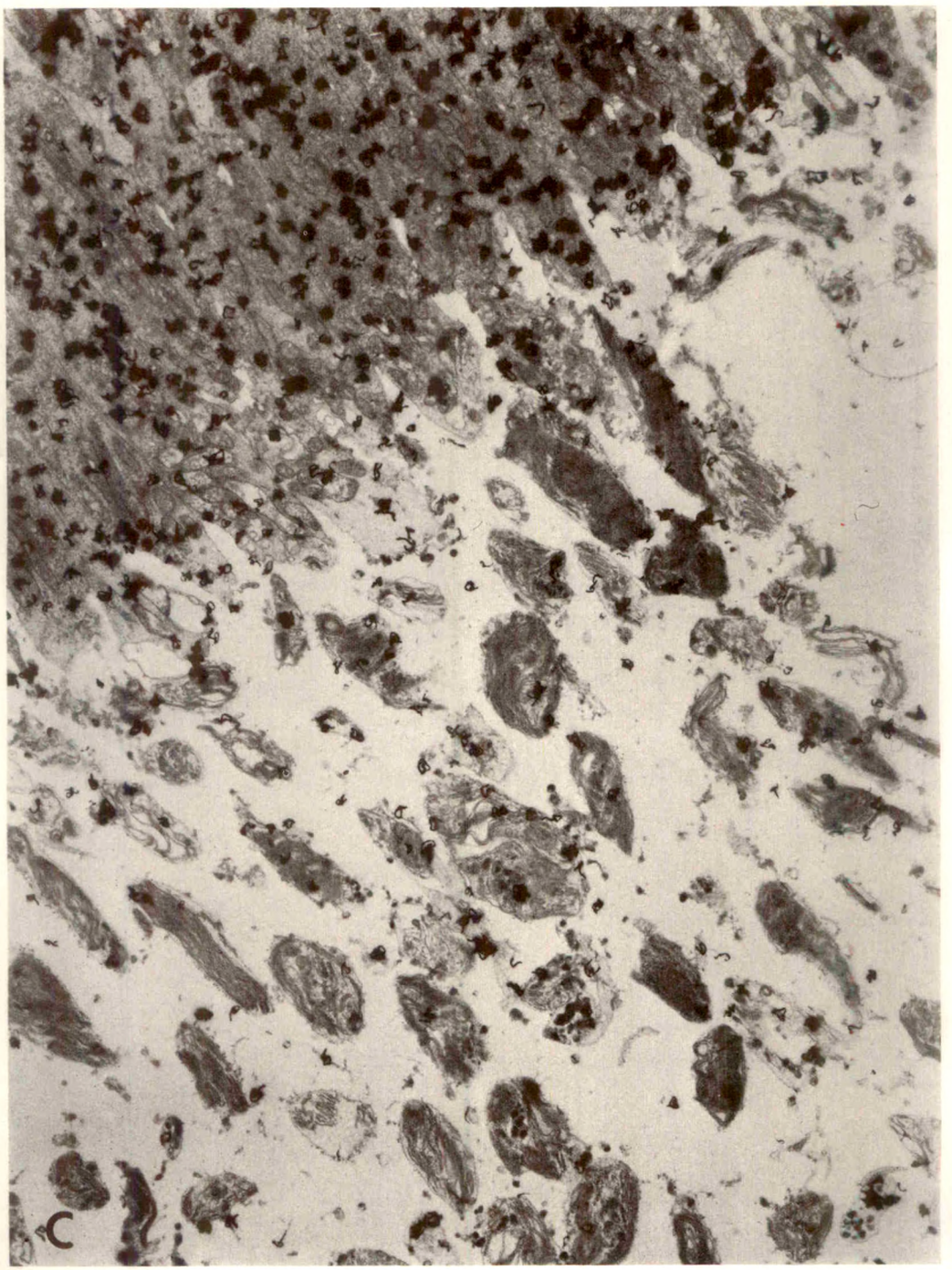



Fig. 1 (Kroll and Machemer). Retinal detachment of four weeks' duration, three hours after surgical reattachment, and two hours after injection of tritiated amino acids. (A) Autoradiography and (B) histology (phase-contrast photomicrographs, ×400). (C, shown on facing page) Electron photomicrograph (×6000). There is extremely heavy labeling of the inner segments (is) compared with the control (Fig. 4). Note close apposition of the retina to pigment epithelium.


C

modification of methods previously described[1-6]: The anesthetized animal was placed in a box with the head projecting. A lateral canthotomy and lateral orbitotomy were done and the conjunctiva opened circumferentially. No diathermy or cryocoagulation was used. The retinal break was localized and appropriate sutures for a radially placed silicone sponge scleral buckling were placed. A drainage site was prepared posterior to the retinal break in the meridian of the planned scleral buckling and subretinal fluid was released using a diathermy needle puncture through choroid and pigment epithelium. A 27-gauge needle on a syringe containing air was passed through the pars plana anterior to the retinal break and into the vitreous cavity. Care was taken to position the eye and head so that both the drainage site and the pars plana injection site were at the lowest part of the eye. With alternating gentle aspiration and injection, the liquified vitreous was entirely replaced by air. The subretinal fluid was thus forced out of the drainage site by the pressure of the intravitreal air. With this method, fluid could be completely drained. The silicone sponge was then placed beneath the sutures and the sutures were tightened and tied. The intravitreal air was finally replaced by saline using gentle aspiration of air and injection of saline.

Each animal then received 55 mc of a tri-

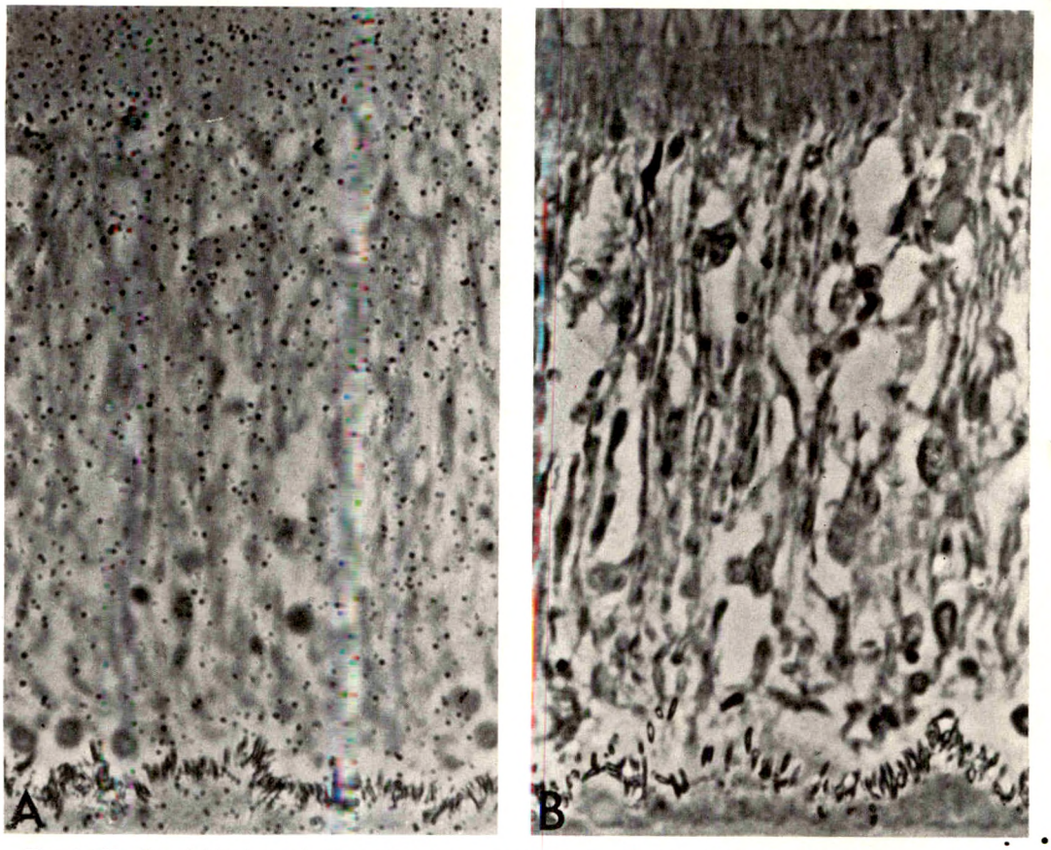



Fig. 2 (Kroll and Machemer). Retinal detachment of four weeks' duration, nine hours after surgical reattachment, and eight hours after injection of tritiated amino acids. (A) Autoradiography and (B) histology (phase-contrast photomicrograph, ×400). (C-facing page) Electron photomicrograph (×6000). M-macrophage. The label has moved diffusely into the outer segments, but is more evenly distributed between inner and outer segments than in Figure 1.


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tiated amino acid solution (50 mc of L-phenylalanine and 5 mc of L-leucine), injected into the ipsilateral internal carotid artery as previously described.[5] Three control animals had similar ipsilateral intracarotid injections. Each control animal had an experimental retinal detachment of four weeks' duration, but in them, no attempt had been made to reattach the retinas. The intracarotid injections were started one hour after reattachment of the retina, and the eyes were enucleated at two hours, eight hours, and two days after the start of the intracarotid injections. Fixation, dehydration, embedding, and preparation for phase-contrast and electron microscopic autoradiographic studies were similar to previous work.[5,7-12] The retina and pigment epithelium situated away from the region of scleral buckling was selected for study.

## Observations

The surgical technique described above permitted immediate reattachment of the retinas with essentially complete drainage of all subretinal fluid (Figs. 1-3). This was accomplished without the use of cryotherapy or diathermy.

For each eye illustrated, a pair of phase contrast micrographs (autoradiography and histology) is accompanied by a representative electron microscope autoradiograph (Figs. 1-5).

The most striking autoradiographic finding was that within three hours of retinal reattachment, there was an extremely heavy labeling of the photoreceptor inner segments as compared with the label of detached retinas (compare Figs. 1 and 4). Nine hours after retinal reattachment (Figs. 2 and 3),

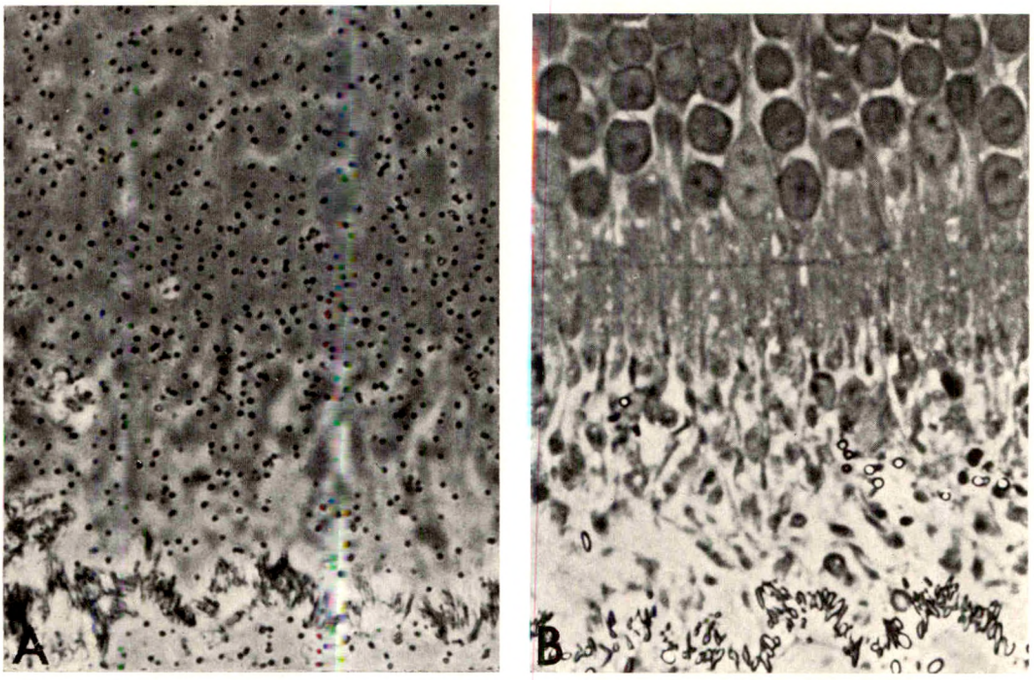
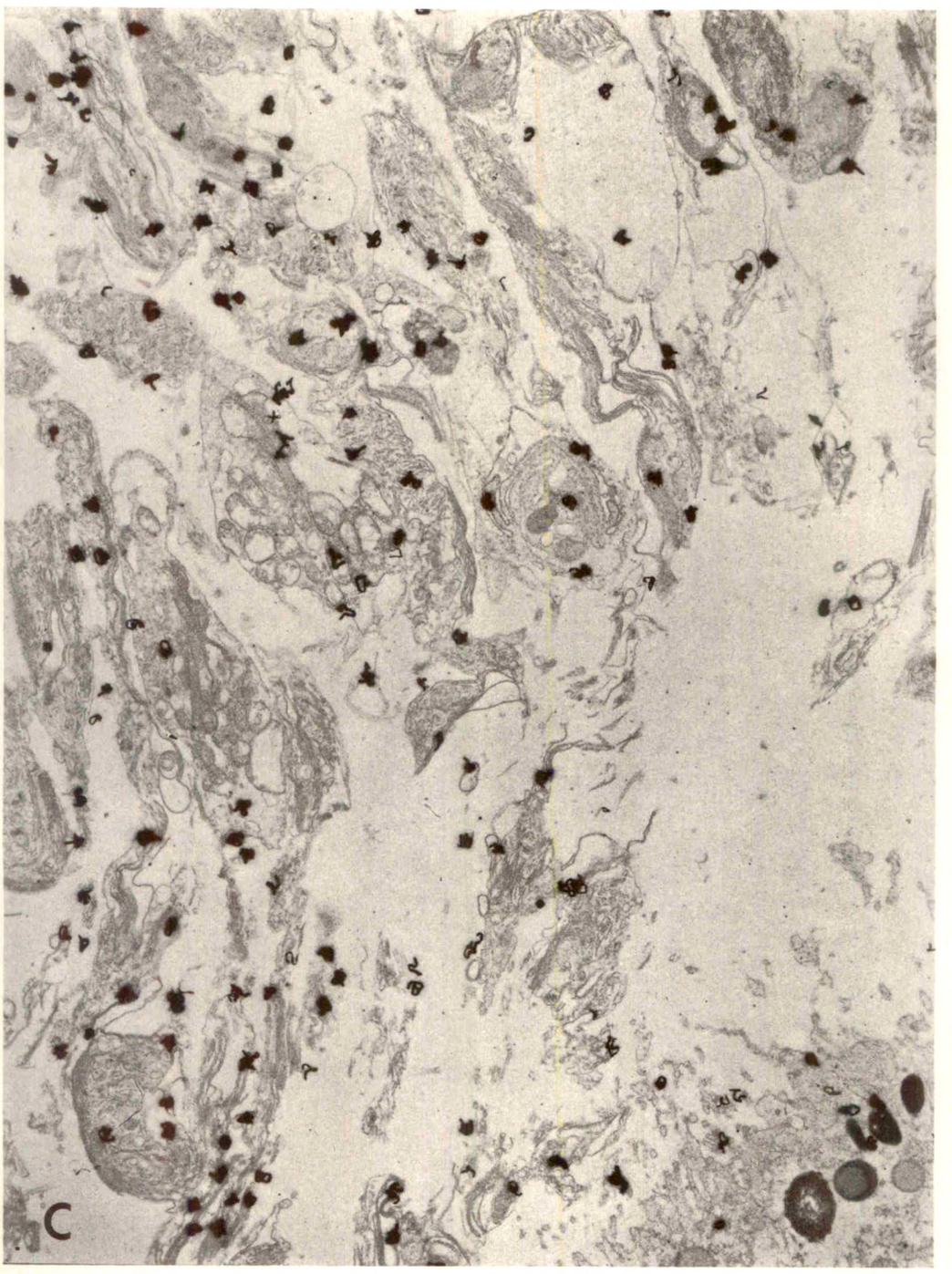



Fig. 3 (Kroll and Machemer). Retinal detachment of four weeks' duration, two days after surgical reattachment, and two days after injection of tritiated amino acids. (A) Autoradiography and (B) histology (phase-contrast photomicrograph, 400). (C-facing page) Electron photomicrograph (×6000). There is no significant change in the distribution of label compared with that shown nine hours after reattachment (Fig. 2). However, the label remains diffuse and heavier than in detached retina (Fig. 5).


C

much of the label had moved diffusely into the outer segments, but unlike normal retina, no banded pattern appeared in the outer segments at that time.[5] Two days after reattachment, one could see heavier labeling of all portions of the photoreceptors than was observed in detached retinas (compare Figs. 3 and 5).

## Comment

The use of intravitreal air tamponade was very effective in removing essentially all subretinal fluid during surgical reattachment of the retina. It was thought essential to drain all of the fluid so as to remove the experimental variable of differing amounts of residual subretinal fluid being present postoperatively. Complete retinal reattachment was histologically confirmed in all cases—in some, as early as three hours postoperatively (Figs. 1-3). The intravitreal air was replaced by saline during the scleral buckling surgery so as to remove the air itself as another variable in the subsequent autoradiographic studies of photoreceptor protein renewal. In addition, so as not to interfere with choroidal or retinal metabolism, no cryotherapy or diathermy applications were made. Despite the lack of cryotherapy or diathermy, all retinas remained reattached during the experiment.

Autoradiographic studies[7-12] have emphasized that normal photoreceptor outer-segment protein is constantly renewed by a process of incorporation of amino acids into protein in the inner segments, a migration of the newly formed protein into the outer segments toward the pigment epithelium, and eventual phagocytosis of the protein by the pigment epithelium.

In a previous study done under identical conditions, the incorporation of radioactive

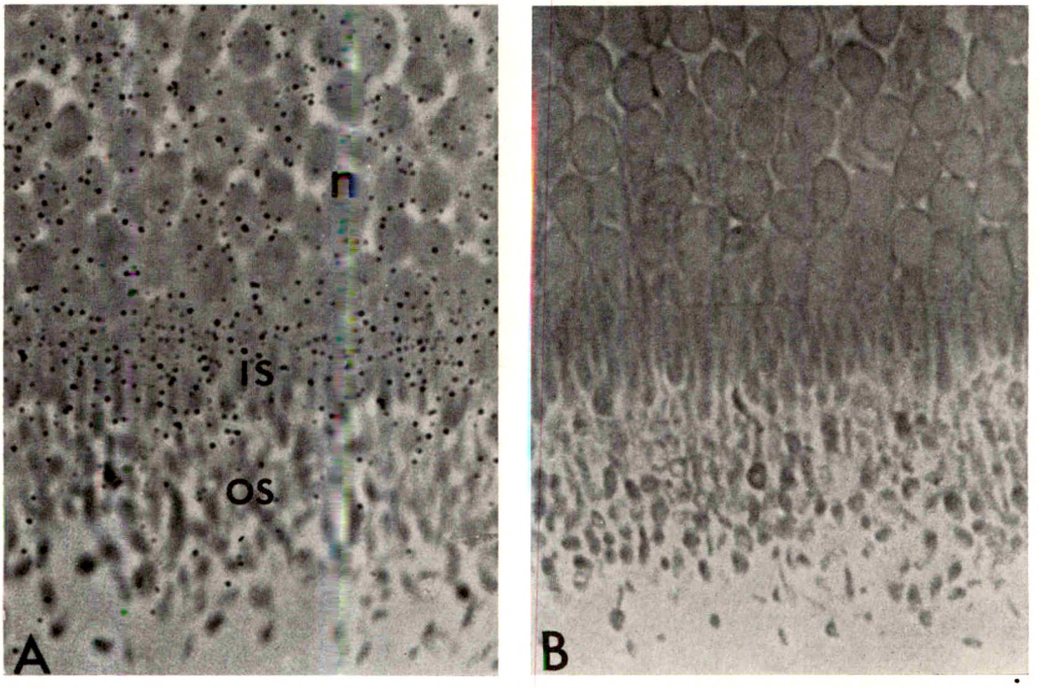
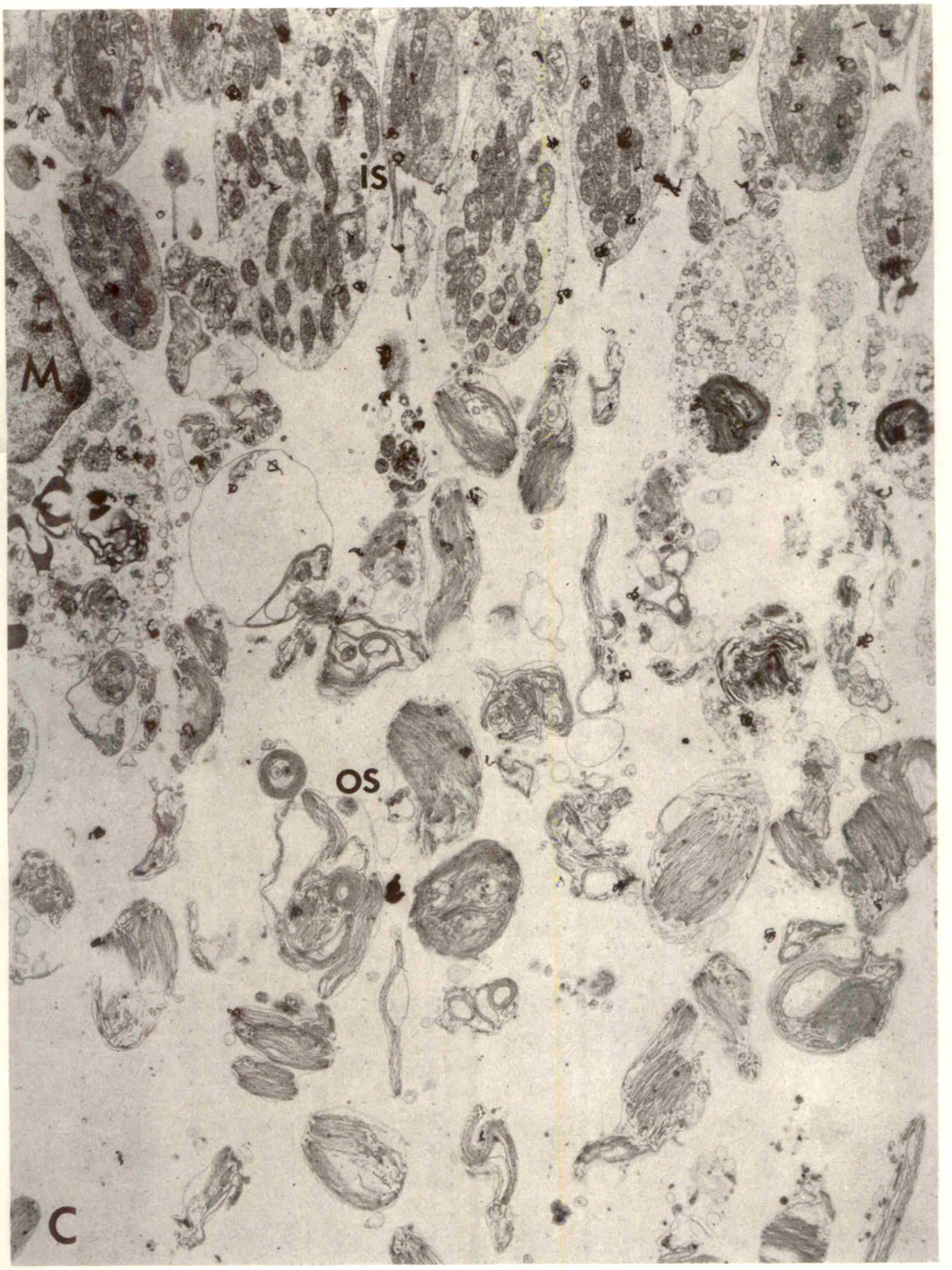



Fig. 4 (Kroll and Machemer). Retinal detachment of four weeks' duration, two hours after injection of tritiated amino acids. (A) Autoradiography and (B) histology (phase-contrast photomicrographs, ×400). (C-facing page) Electron photomicrograph (×6000). The inner segments (is) and nuclei (n) of the photoreceptors are labeled. The outer segments (os) are sparsely labeled. A macrophage (M) also is labeled. This retina serves as a control for the surgically reattached retina seen in Figure 1.


IS
M
OS
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amino acids in normal and detached retinas was demonstrated, and it was shown that retinal detachment does not prevent incorporation of amino acids and the transportation of newly formed protein into the outer segments.[5]

The present study shows that retinal reattachment produces a rapid and marked increase in amino acid incorporation in the photoreceptor inner segment. This incorporation is higher than in the normal, attached retina.[5] Why this occurs is not known; however, the data suggest that, with reattachment, some factor causes amino acid to become more utilized in the photoreceptor inner segment, and triggers this metabolic resurgence. This resurgence probably originates in the pigment epithelium and the triggering factor is either produced or accumulated in these cells. It may be vitamin A, retinene isomerase, or some other substance.

As expected, some time later radioactive protein appears in the outer segment. In the normal eye, there is a band formation with migration from the inner to the outer part,[5,8,12] whereas in the reattached retina, the labeled protein is diffusely distributed all over the outer segment. Even two days after reattachment, there is no hint of a label-free zone in the inner part of the outer segment which one would expect if the protein was deposited in the normal manner. An explanation is difficult, but it is possible that the newly formed protein, after it is exported from the inner segment, can spread widely throughout the relatively "empty" outer segments, whose contents have degenerated during retinal detachment. It is highly unlikely that actual synthesis of outer-segment protein takes place within the outer segments themselves because they lack the synthetic and distributive organelles, the ergastoplasm,

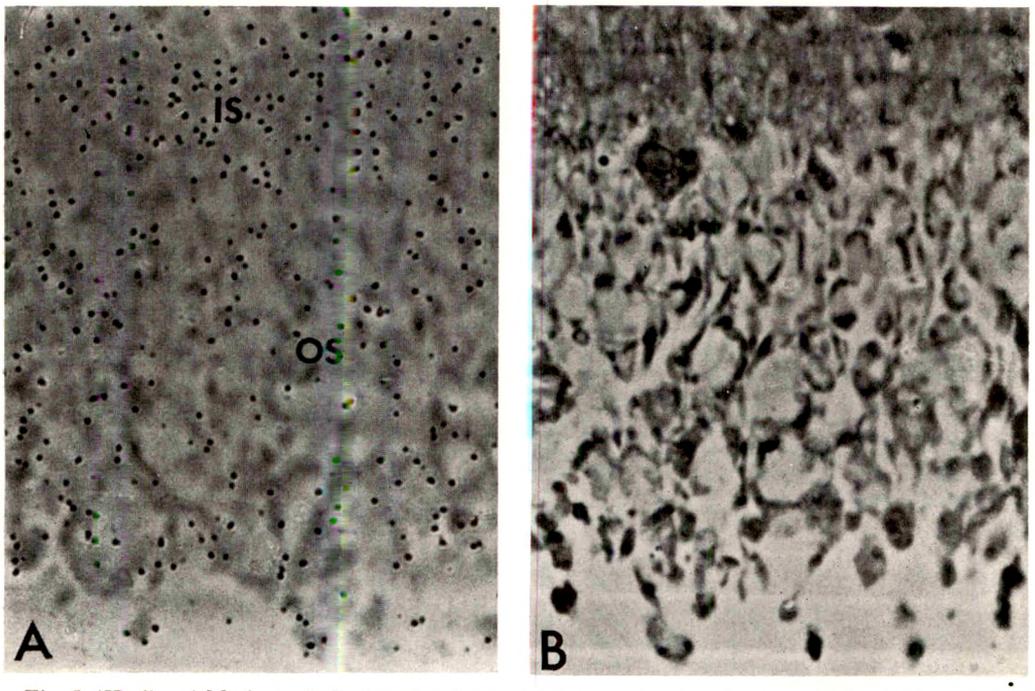
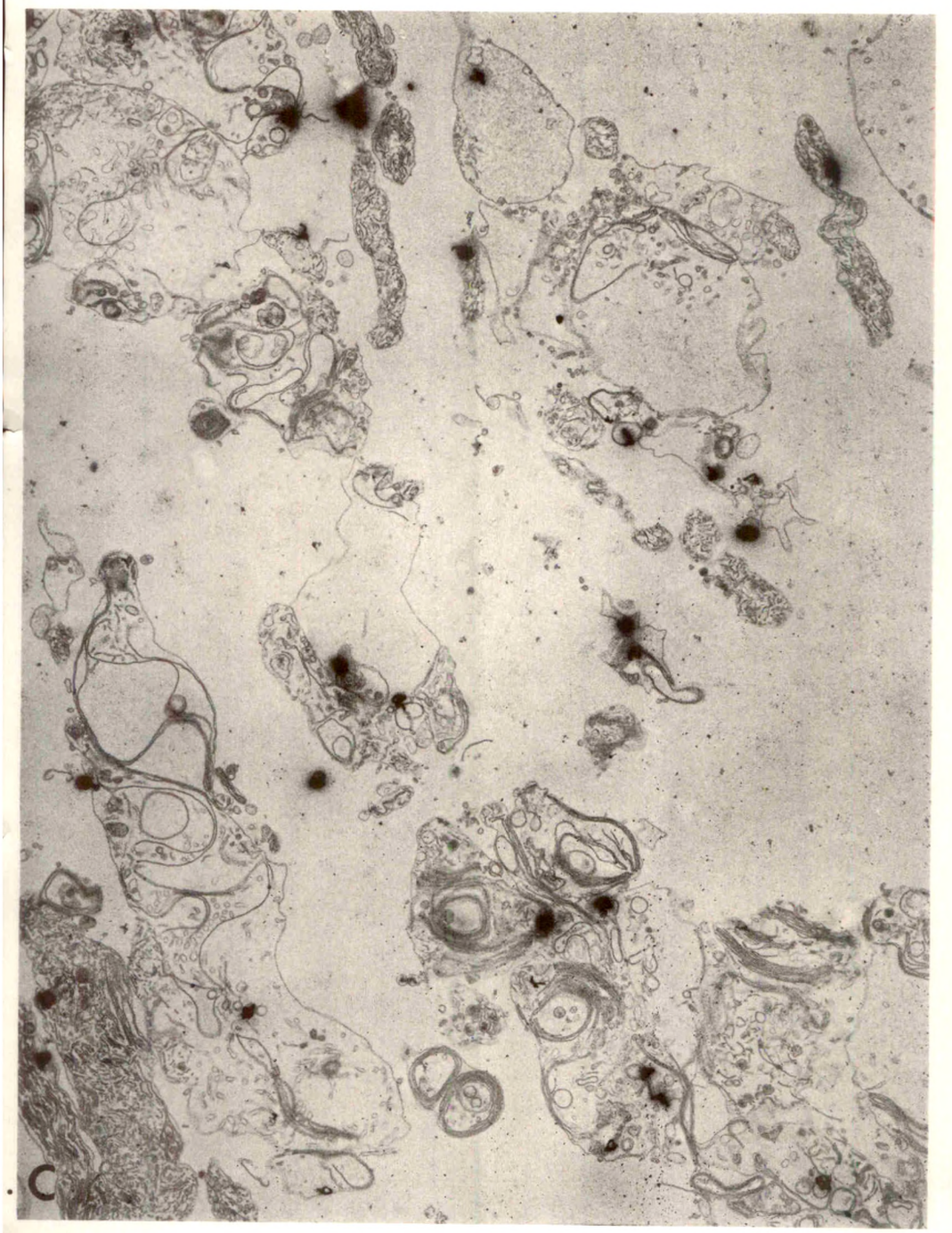



Fig. 5 (Kroll and Machemer). Retinal detachment of four weeks' duration, two days after injection of tritiated amino acids. (A) Autoradiography and (B) histology (phase-contrast photomicrographs, ×400). (C-facing page) Electron photomicrograph (×6000). There is fairly uniform labeling of both inner (is) and outer (os) segments. This retina serves as a control for the surgical reattached retina seen in Figure 3.



and Golgi apparatus, which are in the inner segments.[9] It is unlikely, as well, that the protein—most of which is normally bound to the saccules—should diffuse unbound in the outer segments at a time when abundant sacule material reappears in the outer segment.

Once the outer segment is refilled with saccule material, the random arrangement of saccules will slowly disappear, and after about two days, the normal pattern of stacks of saccules begins to be visible.[2] This suggests a return to normal band formation in the radioautogram, with labeled saccules starting near the inner part of the inner segment.

The high protein metabolism in the photoreceptor layer of the retina after reattachment correlates well with the speed with which the retina recovers functions measured by ERG; the ERG can be recorded as early as five hours after reattachment of the retina.[4]

## Summary

Protein renewal by retinal photoreceptor cells in early retinal reattachment in the owl monkey was studied by phase-contrast and by electron microscopic autoradiography. Compared with detached retina, reattachment produced a rapid, heavy labeling of the photoreceptor inner segments followed later by diffuse labeling of the outer segments. The marked increase in photoreceptor protein metabolism immediately after retinal reattachment correlates well with previous morphologic and electrophysiologic observations of photoreceptor recovery.

## Acknowledgments

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# POSITIVE AND NEGATIVE DEFLECTIONS IN THE OFF RESPONSE OF THE ELECTRORETINOGRAM IN MAN

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The electroretinogram (ERG) is a complex electrical waveform generated by the retina, the start of which, the early receptor potential (ERP), follows almost immediately upon the commencement of a light stimulus. This entire response to onset of illumination —ERP, and a-, b-, and c-waves that follow— is a result of the interaction of the electrical activities of several processes, first described as P-I, P-II, and P-III by Granit[1] in 1947, and since then, further defined[1–7] as to their individual sites of origin and significance.

When the stimulus light is discontinued there is a change in the electrical activity of each of the several processes which make up the total response. The interaction of these processes produces a deflection in the waveform recorded at the surface of the retina or eyeball. This phenomenon, called variously the "off effect," "d-wave," or "off response," has been relatively ignored in the development of electroretinography as a clinical instrument, much greater emphasis having been placed on those responses generated by onset of stimulation. In this paper, we shall use the terms, "on response" and "off response" to mean the alteration in total recorded waveform engendered by onset and cessation of light stimulation.[5]

The off response of the ERG begins with a negative-going deflection in predominantly rod retinas[1–7] and with a positive-going wave in cone retinae.[1–3,5,8]

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The human dual retina would be expected to be subject to variation in its off response from the positive, cone type to the negative, rod type by manipulation of stimulus or adaptation parameters.

The human off response is negative in polarity with a dim stimulus.[9–12] The human off response becomes positive in polarity with increased stimulus intensity,[10,13–16] and is preserved in stationary congenital night blindness.[13,16]

This paper describes the characteristics of the negative and positive off responses in normal human subjects and the variations from normal of the responses in stationary congenital night blindness and rod monochromatopsia. Our goal, in this study, is to lead toward the ultimate utilization of the off response as a clinically useful parameter of the ERG.

## METHOD

Stimulus light from a 1 kw tungsten source was brought to a focus, after transmission through heat filters, at an electromechanical shutter, which controlled the light beam to provide rectangular flashes of 0.74 second duration at two- to 30-second intervals. The stimulus light then entered one of the two input ends of a Y-shaped glass fiber light guide.

Adapting light from an additional tungsten source (150 w) was focused upon the other input end of the light guide. The glass fibers carrying light from each source were mingled together at the output end (7 mm in diameter), which was held 5 cm from the cornea of the examined eye. Zero log unit intensities of stimulus and adapting light were $8.4 \times 10^3$ and $5.2 \times 10^3$ lux, respectively, at the cornea. Neutral density filters were interposed in the light path to decrease the luminance. Stimulus and adapting light

intensity was expressed in $\log_{10}$ units. No adapting light was present, unless noted.

ERG responses were led from a contact lens electrode[17] to a Grass electroencephalogram amplifier (7P511, time constant 0.25 second unless otherwise noted) and averaged by a Mnemotron CAT 400 computer. The combined earlobes served as the indifferent point. The pupil was dilated with 1% tropicamide. Upward deflection indicates positivity of the corneal electrode.

## Results

A very dim stimulus (−4.0) evoked a small b-wave (one of the on responses) and a negative off response (Fig. 1). The threshold of the negative off response was the same as that of the b-wave. With increasing stimulus intensity (up to −2.0 log units), the b-wave amplitude rapidly increased, while the negative off response increased only slightly. Further increase of stimulus intensity decreased the amplitude of the negative off re-

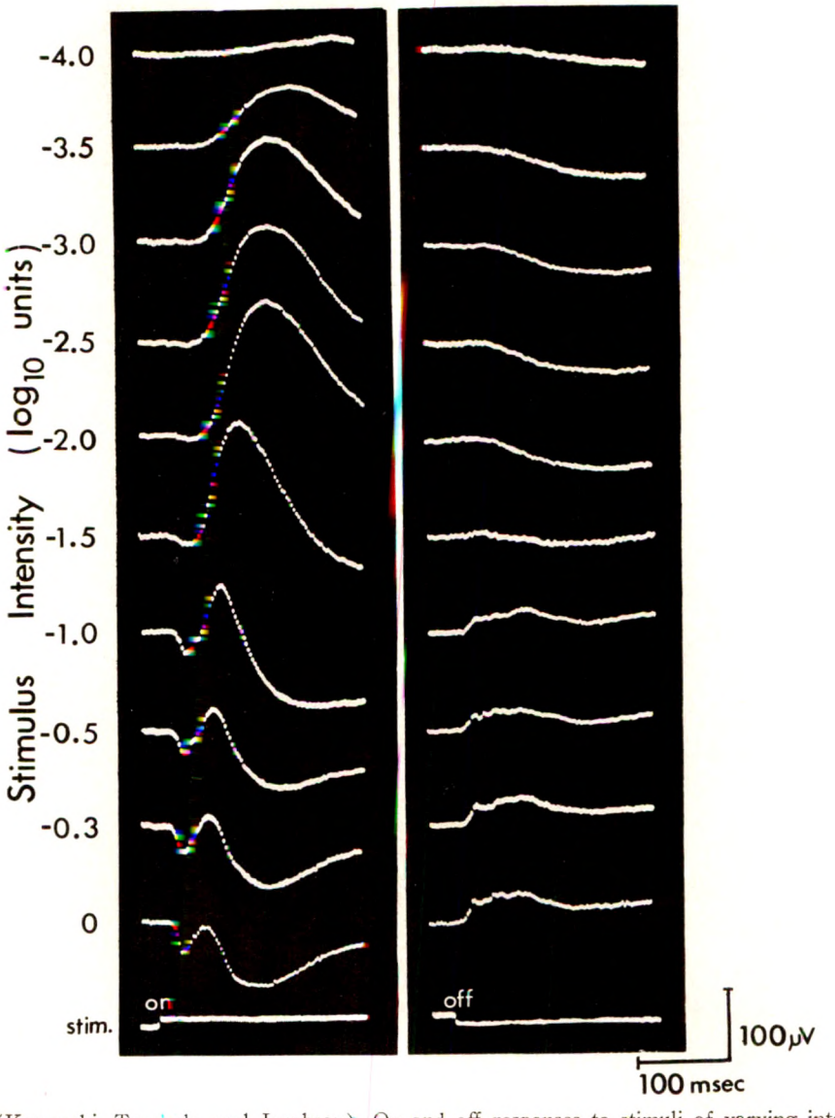



Fig. 1 (Kawasaki, Tsuchida, and Jacobson). On and off responses to stimuli of varying intensities in normal subject. Each trace is average of 20 responses. Stimulus frequency 0.5 Hz.

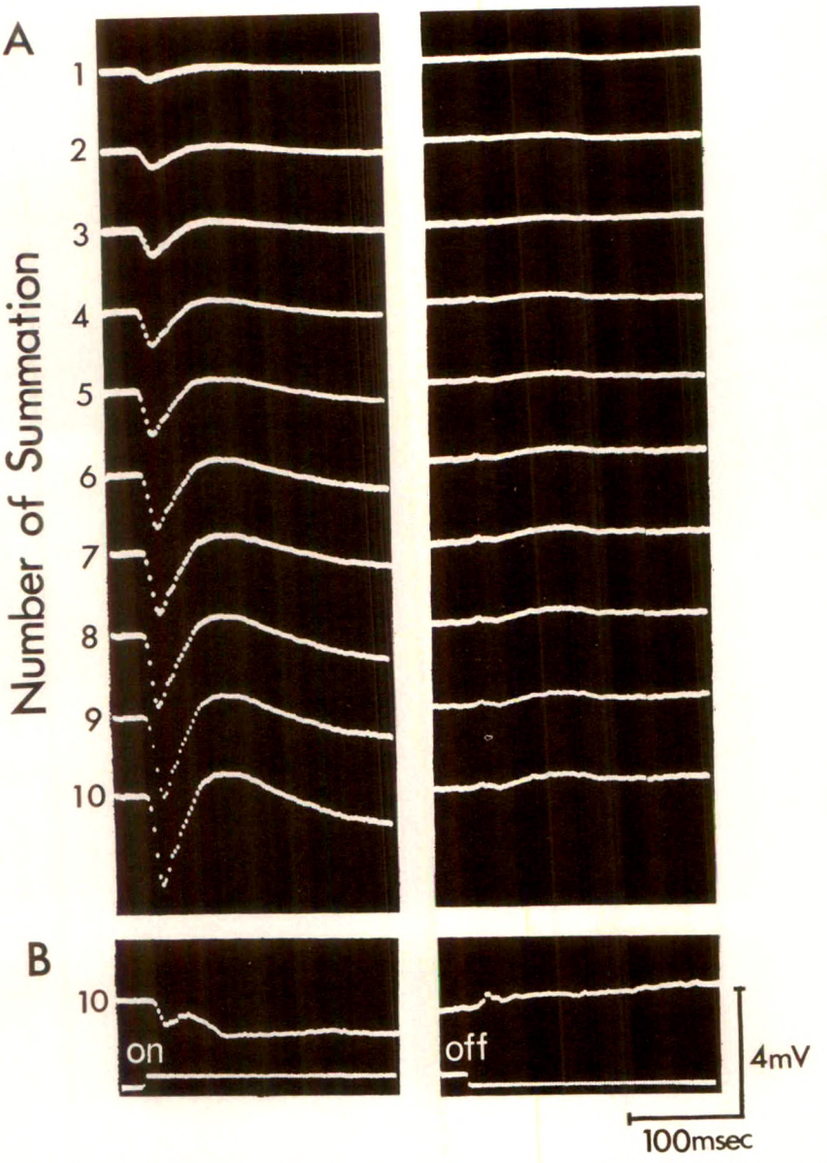



Fig. 2 (Kawasaki, Tsuchida, and Jacobson). On and off responses of normal subject to (A) intense stimulus (zero log unit) in virtually dark-adapted state and (B) in light adaptation induced by high frequency of stimulation. In A, after dark adaptation of 30 minutes, 10 stimuli were delivered at a rate of one flash per 10 minutes, with no background illumination between flashes. Responses to these 10 stimuli were successively summed. In B, 10 identical stimuli were presented once a second, with no preliminary dark adaptation. Summed response to these 10 stimuli shown. Vertical calibration relates to sum of amplitudes of responses.

sponse, which was now preceded by a small positive off response (−1.5, Fig. 1). With still brighter stimuli, the amplitudes of the a-wave and positive off response increased approximately linearly to log stimulus intensity, while the b-wave was suppressed. The positive off response was followed by a negative-going wave returning toward the baseline.

The apparently paradoxical reduction of

b-wave amplitude with increased stimulus intensity is partly due to the increased level of light adaptation consequent to the use of repetitive stimuli necessary for computer averaging. This light adaptation may also influence the positive off response. In an attempt to control this factor, the series of experiments illustrated in Figure 2 was conducted. The subject was dark-adapted for 30 minutes, then exposed to 10 single stimuli of maximum intensity, one flash every 10 minutes, with no background light between flashes. The summed a- and b-wave amplitude of these 10 responses was equal to 10 times the amplitude of the first dark-adapted response. Inspection of the individual responses (not summed) revealed no difference in a- or b-wave amplitude between the first and last responses. Since a- and b-wave amplitude is known to be sensitive to light adaptation, this would indicate that dark adaptation was not significantly affected by this set of stimulus parameters. In this situation the positive off response was very small (Fig. 2-A). In Figure 2-B, the stimulus of the same intensity as used in Figure 2-A, was repeated once every second. Light adaptation engendered by this frequency of stimulation—and indicated by the reduced a- and b-wave amplitude—was accompanied by an increase in the positive off response. Therefore, light adaptation induced by the repetitive stimuli augments the positive off response.

Figure 3 shows the effect of increasing light adaptation on responses to a relatively dim stimulus (−3.0). Increased level of light adaptation alone did not produce a positive off response unless the stimulus was sufficiently intense. Repetitive, intense stimuli, hence, are favorable to positive off response production.

The spectral sensitivity of the b-wave,

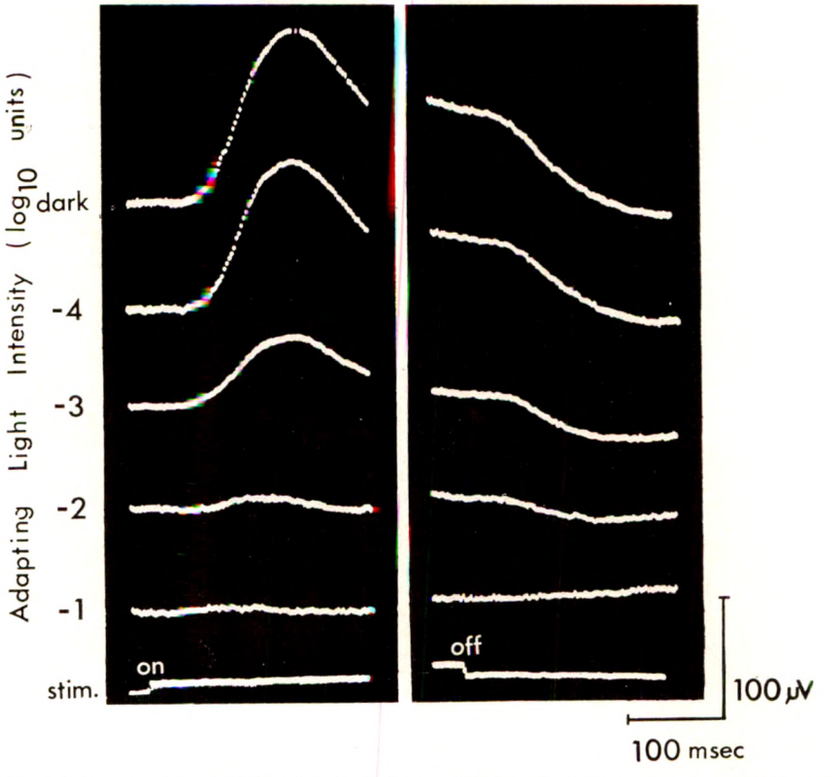



Fig. 3 (Kawasaki, Tsuchida, and Jacobson). Effects of light adaptation on the on and off responses to dim stimulus (−3.0 log unit) in normal subject. Average of 20 responses. Stimulus frequency 0.5 Hz.

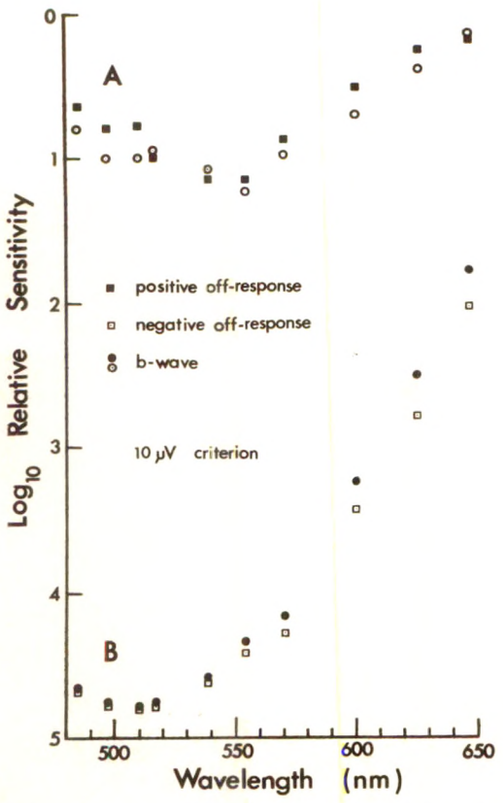



Fig. 4 (Kawasaki, Tsuchida, and Jacobson). Spectral sensitivity of b-wave, positive and negative off responses. (A) Eye was exposed to adapting light of —1.1 log unit. (B) No adapting light was used, but eye was dark-adapted for 30 minutes prior to recording. Stimulus intensity was increased in 0.5 log steps from sub-threshold level at each wave length of equal intensity monochromatic light. Ordinate is $\log_{10}$ reciprocal stimulus intensity required to evoke response of 10 μv criterion voltage. Data derived from average of 80 responses in A and of 20 responses in B. Stimulus was repeated every two seconds in A and 30 seconds in B.

positive and negative off responses was studied using a series of equal energy monochromatic stimuli obtained by use of interference filters and neutral density filters. The eye was dark-adapted for 30 minutes prior to the recording. Stimulus intensity was increased in 0.5 log steps from subthreshold level at each wavelength.

Precautions were taken to avoid disturbing dark adaptation during the recording: Relatively dim stimuli were used, the maximum intensity being not more than one log unit above the intensity producing a just discernible b-wave at each wavelength. Dark adaptation of 10 minutes was allowed between recordings at different wavelengths. Stimuli were repeated at low frequency (one flash every 30 seconds).

The amplitudes of the averaged responses were plotted versus log stimulus intensity at each wavelength. From such graphs we derived the stimulus intensity required to produce a constant (10 μv) amplitude response at each wavelength. The reciprocal of the resulting intensity value represents sensitivity. The spectral sensitivity curves thus obtained are illustrated in Figure 4. The low-threshold negative off response was as sensitive to monochromatic light as the dark-adapted b-wave, and its spectral sensitivity approximately fitted the C.I.E. scotopic sensitivity curve[18] in dark adaptation.

The spectral sensitivities of the positive off response and the b-wave were obtained similarly. The eye was light-adapted to white light of −1.1 log unit intensity so as to saturate the scotopic function.[19] Since, with this constant background illumination, light adaptation induced by repetitive stimuli became less significant, stimuli were repeated at high frequency (one flash every two seconds) for averaging. The positive off response and b-wave thus light-adapted were the most sensitive to light of a wavelength of about 550 nm (Fig. 4).

Figure 5 is the ERG of a 59-year-old white man with recessively inherited stationary congenital night blindness. His dark adaptation curve showed only the cone portion. Color vision was normal. He was myopic and corrected vision was 20/30 in each eye. The fundi showed peripheral retinal atrophy, myopic crescents, and narrowing of retinal arteries. Neither b-wave nor negative off response was evoked in this patient by −3.0 log unit stimulus, which was bright enough to elicit these responses in normal subjects. Intense stimuli evoked an a-wave and a

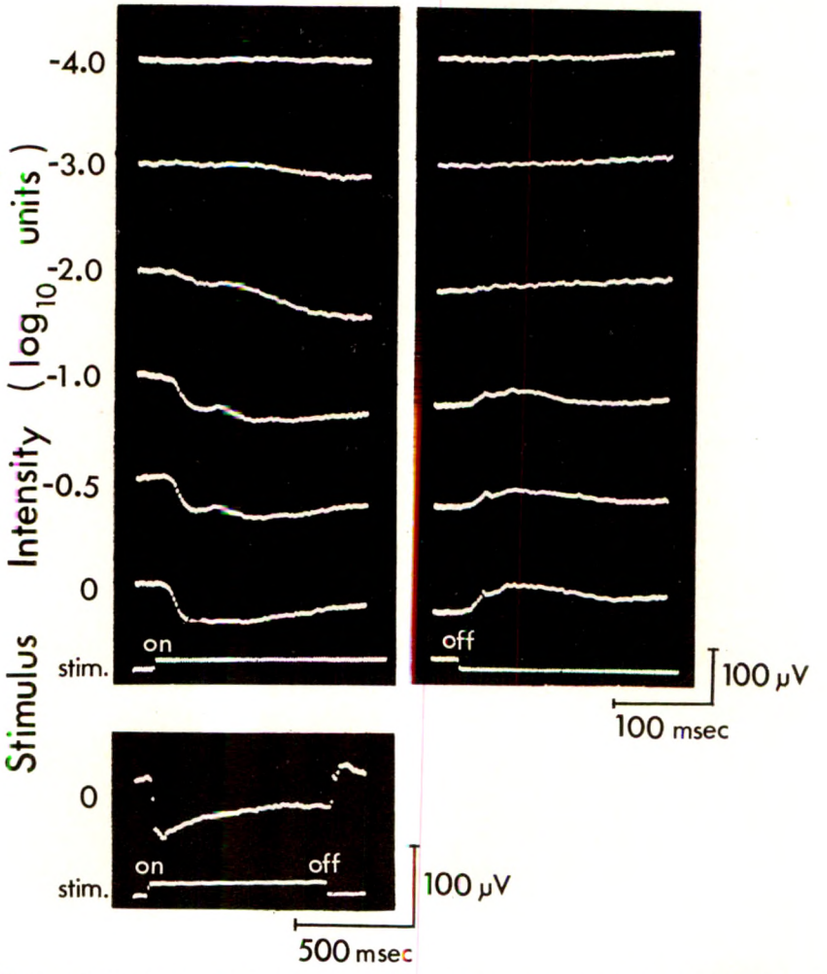



Fig. 5 (Kawasaki, Tsuchida, and Jacobson). ERG in stationary congenital night blindness. On and off responses absent with dim stimulus, a-wave and positive off responses present with bright stimulus. Average of 20 responses. Stimulus frequency 0.5 Hz. Amplifier time constant 0.6 seconds in lowest record in left column, 0.25 seconds in all other records.

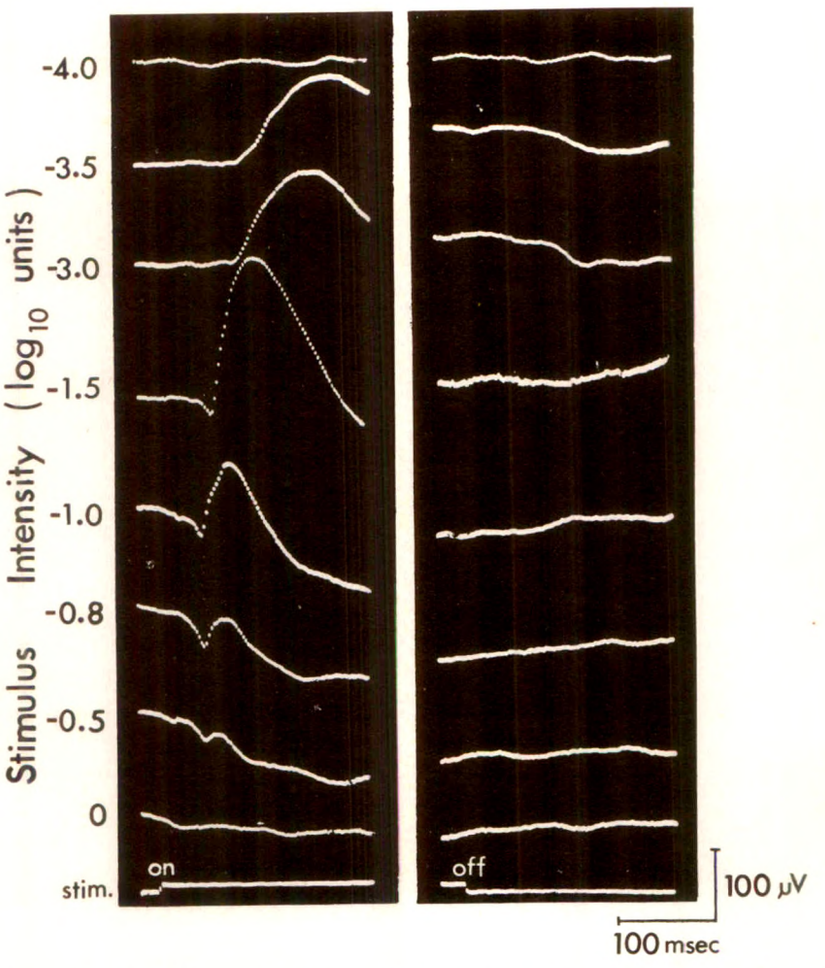



Fig. 6 (Kawasaki, Tsuchida, and Jacobson). ERG in rod monochromatopsia. Negative off response present, positive off response absent. Average of 20 responses. Stimulus frequency 0.5 Hz.

positive off response of normal amplitude, but b-wave amplitude was greatly decreased. The ERG, hence, appeared to consist of P-III[1] or the late receptor potential[2,3,5] (lowest record, Fig. 5).

The level of light adaptation induced by the repetitive stimuli of −3.0 log units (8.4 lux) should not exceed the level which is equivalent to continuous light adaptation of this intensity (8.4 lux), since dark periods intervene between repetitive stimuli. The level of adaptation produced by continuous light of 8.4 lux is below the saturation level of the human scotopic function.[19] Therefore, the absence of the low-threshold negative off response with this stimulus intensity in this patient is not due to the suppression of the scotopic function by light adaptation induced by the repetitive stimuli.

Figure 6 shows the ERG of a five-year-old white girl with poor vision (20/200 in each eye), photophobia, nystagmus, and poor color vision. The fundi were normal. Color tests, including Ishihara, H-R-R pseudo-isochromatic plates, and anomaloscopy, in conjunction with her symptoms, indicated that her color defect was rod monochromatic. We found the low-threshold negative off response present and the high-threshold positive off response unrecordable in this pa-

tient. The positive off response was absent in this case even with a stimulus bright enough to evoke a distinct a-wave in normal subjects. General anesthesia was used in this patient because she could not tolerate bright stimulus lights. The anesthesia was not responsible for the absence of the positive off response in this case, however, since a normal positive off response was found under identical general anesthesia in normal subjects.

## Discussion

If the analyses of animal ERGs[1-3,5,20] may be applied to the human ERG, the low-threshold negative off response would represent the termination of P-II[1] or the dc component,[20] and the initial ascending phase of the high-threshold positive off response the end of P-III or the late receptor potential.[2,3] Studies of animal ERGs[4,20] also suggest that the negative-going wave following the high-threshold positive off response is due to the end of P-II[1] or the dc component. A positive plateau potential, which seems to correspond to the dc component of the cat,[20] is also present in man.[12,21]

Evidence suggests that reduction of the amplitude of the negative off response at moderate stimulus intensities, similar to that seen at the transition from the negative to positive off effect in Figure 1, occurs in single flash studies,[11,12] indicating that this phenomenon is not due to light adaptation induced by repetitive stimuli. One of the possible explanations for this amplitude reduction of the negative off response is that the positive off response adds algebraically and results in an apparent decrease in amplitude of the negative off response.

Figure 4-B indicates that the low-threshold negative off response is mediated by the rod system in dark adaptation. The absence in night blindness and the presence in rod monochromatopsia (Figs. 5 and 6), of this low-threshold negative off response, favor this assumption.

The presence in night blindness, and the absence in rod monochromatopsia, of the positive off response (Figs. 5 and 6), suggest its close relationship with the cone system. This assumption is supported by its high threshold and spectral sensitivity. Our results do not exclude the possibility of the contribution of the rod system to the positive off response in the fully dark-adapted state.[22] Dark-adaptation should increase the amplitude of an ERG response related to the rod (scotopic) system. The positive off response is larger in moderate light adaptation than in dark adaptation[15,16] (Fig. 2). This suggests that the rod system does not greatly contribute to the high-threshold positive off response.

## Summary

When stimuli of relatively low intensity are used, the off response of the human electroretinogram consists mostly of a negative-going wave. With intense stimuli, the off response begins with a positive-going wave. The negative-going wave of the off response to dim stimulus is absent in stationary congenital night blindness and present in rod monochromatopsia. The positive-going wave of the off response to intense stimulus is present in stationary congenital night blindness and absent in rod monochromatopsia.

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OPHTHALMIC MINIATURE

It is a widely spread belief that there is a strange power in the eyes of man. Mowgli was expelled from the wolf pack because they could not bear his gaze, and even his best friend, the panther, was unable to look him straight in the eyes. . . . Amongst themselves, animals only look at each other fixedly when they intend to take drastic measures or are afraid of each other. Consequently they conceive a prolonged fixed gaze as being something hostile and menacing and rate it in man as the expression of extreme malevolence. And this the whole secret of the "power of the human eye."

Konrad Lorenz
*Man Meets Dog*
Methuen & Co. Ltd., 1954

# BANDAGE LENSES IN THE TREATMENT OF BULLOUS KERATOPATHY

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In a previous paper[1] we reported that hydrophilic contact lenses provide a simple and often useful therapy for bullous keratopathy. These lenses* (Griffin) can be worn in cases of epithelial bullae and gross corneal irregularities without causing corneal ulceration. They generally relieve the pain associated with ruptured bullae and corneal ulcers without interfering with the healing process. Their use as an optical bandage for diseased corneas has improved vision and relieved pain in many cases where other sight-preserving techniques have failed or were not possible.

Since our original report, we have fitted a total of 528 corneas (normal and pathologic) with bandage lenses and have monitored an additional 1207 cases fitted by other clinicians. A review of these data corroborated our previous results and revealed that errors in fitting can cause poor results as well as unnecessary complications.

Our present fitting techniques are presented here, together with a summary of the clinical results of this therapy in 49 patients with varying degrees of bullous keratopathy.

## MATERIAL AND METHODS

Through studies of the Bausch and Lomb, the Griffin, and other types of lenses, we found that good visual results required the use of lenses available in various curvatures and diameters. Leibowitz and Rosenthal[2] similarly reported relief of pain without improvement of vision with the Bausch and Lomb lens. For this reason, only Griffin lenses were used as bandage lenses in this study.

*The lens*—A detailed description of the Griffin lens has been presented elsewhere.[1] Briefly, it is both flexible and hydrophilic, containing a high water content and reasonably good optical surface and a tear layer beneath the lenses. The Griffin lens potentiates the action of medication such as hypertonic saline, and it is available in a variety of diameters and curvatures, which may explain, in part, the superior visual acuity obtained with theses lenses.

*Fitting procedure*—Fitting patients with bullous keratopathy is much more difficult than fitting patients for simple refractive errors. However, experience in fitting patients for refractive errors is a significant asset in fitting pathologic corneas.

Trial lens fitting is the easiest and often only method by which these lenses can be fitted in patients with bullous keratopathy. Through such testing, the dimension, curve, and diameter that will give the best and most stable performance is determined. A properly fitted lens has both central and peripheral contact, so that it does not flex in the center with each blink, and it has sufficient diameter so that it will not move with each blink. However, it is difficult to verify this alignment for any given lens. Fluorescein is useless since it penetrates the lens instantly and does not delineate the form of the tear layer. In addition, keratometer readings are usually unavailable in patients with bullous keratopathy. Thus the first question is how to select a lens that will provide sufficient adherence to prevent movement without inducing too much apical clearance and, consequently, variable vision.

If the lens selected is not of the proper curvature and diameter, there are two possible difficulties: it may be too steep, or it may

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* Still available only for investigative use.

be too flat. If the lens is too flat (or too small), it will move up and down with each blink or will be displaced laterally on sideward gaze. If the lens is too steep, there is alternate blurring and clearing of vision with each blink. This may be somewhat difficult to evaluate initially in a patient with bullous keratopathy. However, if there is any doubt that the lens might be steep, one should proceed to the next flatter lens (or the one with the next smaller diameter). If the lens is too flat, it will move excessively. If the lens moves too much one can be assured that the proper lens is steeper. If the lens seem to center properly in the eye, one can try for a flatter lens to be certain that it is not too steep.

The following guidelines have been extremely helpful to us in selection of the proper combination of curve and diameter for any given patient:

1. A larger diameter increases adherence and may cause apical clearance.
2. A smaller diameter decreases adherence and may cause movement and lag.
3. A steeper curve increases adherence and may cause apical clearance and associated change in vision.
4. A flatter curve reduces adherence and will eliminate the changing vision caused by flexing of the lens.
5. Never rely on the results of a given test lens until the lens has been on the eye for a significant amount of time (15 to 30 minutes).

This last rule is most important in patients with bullous keratopathy. Large, single bullae usually disappear within a few days, and only diffuse epithelial edema remains. The constant wearing of these lenses also results in dehydration of the cornea and a significant change in corneal shape. The lens that fitted properly before is no longer satisfactory. This change usually results in a reduction in visual acuity, and it is not unusual to find a patient with an initial visual improvement from 20/200 to 20/40 in whom, after a few days, visual acuity decreases to 20/100 or 20/200. Biomicroscopy of the eye usually reveals a significant change in the cornea with disappearance of the big bullae and diffuse epithelial edema. When these cases are refitted and hypertonic saline used, visual acuity usually improves again. In some cases several changes in the lenses are required.

Once the proper curve and diameter are determined, the refractive power of the lens should be considered. For the beginner, plano lenses will simplify the procedure. The proper power can be prescribed by one of the following techniques:

1. By using the spectacle refraction and vertex distance and refining the refraction through a trial lens procedure.
2. By using plano lenses and refracting over.

The selection of the trial lens is mady by taking the spectacle refraction in minus cylinder form, ignoring the cylinder and correcting for the vertex distance when necessary.

Just as the base curve of the lens changes with changing corneal curvature, the required refractive power may change. Patients with bullous keratopathy must have over-refraction in each follow-up visit.

*Use of medications*—Pupils are dilated for the first few days in cases of chronic bullous keratopathy, especially with epithelial defects, because of the concomitant iritis present in almost every case. We have found it extremely useful, in many cases of chronic bullous keratopathy, to institute eyelid hygiene techniques. Hexachlorophene (pHisoHex) scrubs for five minutes once or twice a day have virtually eliminated minor infection and unrecognized blepharitis as causes of patient discomfort.

Antibiotics are used if secondary infection or chronic blepharitis is present at the time of fitting.

Five percent hypertonic saline without

preservative or methylcellulose is the single most important medication used in combination with the lenses. In most cases it produces a significant improvement in vision and is used three to five times a day, as necessary. However, it should be avoided initially in patients who have a significant amount of discomfort. In these cases, lens application and pupillary dilation should relieve the pain within a few days. At that time the patient should be refitted and hypertonic saline used for improvement of visual acuity.

The following variations in technique have been used:

1. In advanced cases of bullous keratopathy where a hazy subepithelial layer is present, the pathologic corneal epithelium and the underlying connective tissue are easily removed after application of local anesthetics with a cotton swab or a No. 15 Bard-Parker blade. Homatropine, atropine, or scopolomine is then applied to the eye. Neosporin ophthalmic solution is also generously applied to the eye. A pressure patch is not necessary in these cases where the lens is inserted immediately after the removal of the pathologic corneal epithelium. Visual acuity is usually much improved immediately after such procedures, but it will decrease one or two lines after a few days. This is due to the regrowth of the corneal epithelium, the thickening of the corneal stroma, and, in some cases, folds in Descemet's membrane. The lens must be refitted in all these cases and application of 5% hypertonic saline instituted once the eye is comfortable.

2. In patients with advanced bullous keratopathy and some subepithelial membrane, no effort should be made to fit with the proper refraction until several weeks after the lens is applied. In these cases, a plano lens of the proper diameter and base curve is used.

3. In patients with a large epithelial defect, such as after removal of an epikeratoprosthesis,[3] the pupil is dilated and a randomly selected, preferably steep lens and antibiotics are applied to the eye. The lens is left in the eye until re-epithelization has occurred. We prefer to allow two to four weeks before any attempt is made to improve visual acuity by refitting the patient.

4. If the proper lens dimension cannot be determined at the first visit, we have found that an 8.1 lens 14.0 mm in diameter with central thickness of approximately 0.3 mm gives the most satisfactory result until the proper dimension can be determined.

## Results

Between February, 1969, and July, 1970, a total of 49 patients with varying degrees of bullous keratopathy have been fitted with bandage lenses at the University of Florida.

Of these 49 patients, 41 are still wearing their lenses. In eight in whom use of the lens was discontinued, only one significant lens-related complication has occurred. One patient developed a purulent conjunctivitis. The lens was erroneously left in the eye for a week and a small corneal ulcer developed. This healed rapidly under treatment without visual loss, and lens wear was resumed. The most common reason for discontinuing the lenses was failure to improve the visual acuity to a reasonable level in patients who had no significant discomfort. Of the 41 patients still wearing the lenses for relief of pain and improvement in vision, 12 have now worn them for over one year; the other 29 have worn them from three to twelve months.

*Visual acuity*—In most cases visual acuity was counting fingers prior to bandage-lens therapy. A few patients had a visual acuity better than 20/100 and only one was as good as 20/60.

The improvement in visual acuity after treatment with the Griffin lenses is shown in Table 1. It is, however, based on the following considerations:

Visual acuity is often improved immediately after insertion of the lens and the application of hypertonic solution. However, in some cases, many fittings and several weeks or even months are necessary before the best visual acuity can be obtained.

TABLE 1

BEST VISUAL IMPROVEMENT AFTER BANDAGE-LENS THERAPY

| Visual Acuity | No. Cases |
|---|---|
| 20/20 | 9 |
| 20/40 | 12 |
| 20/60 | 2 |
| 20/80 | 1 |
| 20/100 | 9 |
| 20/200 | 5 |
| Less than 20/200 | 11 |

Visual acuity improves after the application of 5% hypertonic saline without preservative. An effective schedule for its application seems to be one or two drops on awakening and repeated applications at 10:00 A.M., 1:00 P.M., and 5:00 P.M. Hypertonic saline is most needed during the morning hours. In the afternoon, visual acuity clears somewhat even without the application of hypertonic saline.

Visual acuity may fluctuate. Therefore, the patient must make a hypertonic saline schedule that best fits his individual requirements. In bilateral bullous keratopathy cases under bandage-lens therapy, visual acuity fluctuates at different times in each eye, and these patients seldom complain of fluctuating visual acuity. In monocular cases, the variations are more noticable, but this is not a significant problem if the patient learns the proper use of hypertonic saline. It must be emphasized early in treatment that there is no limitation to the number of installations of hypertonic saline needed.

An unexplained decrease in visual acuity should be checked by over-refraction or refitting of the lens. In several cases, refraction and corneal curvature changed after several days or weeks of therapy. In all cases, refitting for the proper lens dimension and power has resulted in improvement of visual acuity. Post-cataract macular edema is seen in these patients. Fluorescein angiography has frequently indicated this explanation for vision which could not be improved.

*Relief of pain*—The combination of bandage-lens therapy and pupillary dilatation have resulted in rather uniform relief of the pain of bullous keratopathy. It must be emphasized, however, that in painful advanced cases there is always a concomitant ciliary spasm. The intelligent use of dilating drops is necessary.

In some chronic cases, it is not unusual for the application of hypertonic saline to be painful at first, and since this significantly disturbs successful lens wearing, it should be delayed until irritability has ceased and the patient is ready for refitting.

Elevation of intraocular pressure or glaucoma is often difficult to diagnose in cases of bullous keratopathy. We have found Goldmann and Schiøtz readings inaccurate and misleading in these cases; however, the MacKay-Marg electronic applanation tonometer provides clinically useful measurements and has proven a valuable tool in controlling pressures in these cases.[4]

*Wearing time*—Although 24-hour, continuous wearing time seems to be preferable in most cases of bullous keratopathy, every patient should be individually managed. The full-time wearing of the lenses generally affords the most comfort, and in the beginning we had many cases in which patients experienced pain from ruptured bullae at night when the lens was not in place. In addition, insertion and removal of the lens by unskilled hands seems to produce a significant amount of discomfort and sometimes trauma to the epithelium. Most patients wear the lens for at least a month at a time, and need not manipulate the lens themselves at all. Despite this, however, every patient must be able to remove the lens or have the lens removed in case conjunctivitis develops or the eye becomes red.

## DISCUSSION

Well-planned basic laboratory research is generally easy to interpret. In this type of clinical research, however, there is always the possibility that in spite of the most stren-

uous attempt to avoid it, some prejudice may affect results. The findings of this investigation are as objective as we could make them. As a control, several investigators with different backgrounds were asked to study the effect of Griffin lens therapy in bullous keratopathy.[5] They obtained generally similar results.

The fact that most patients who were fitted a year ago are still wearing the lenses with complete comfort and a sustained improvement in visual acuity indicates that this mode of therapy is clinically useful. Although the improvement of visual acuity is unpredictable in cases of advanced bullous keratopathy, there are few contraindications to trying this simple therapy. If it proves unsuccessful, lenses can be easily removed without risk of permanent damage or great expense to the patient; in our hands, this therapy has proved almost risk free.

The unique synergistic effect of the hypertonic saline and the Griffin lenses appears to stem from the absorption and gradual elution of drugs from these lenses.[6] Other hydrophilic contact lenses such as the Bausch and Lomb lens do not seem to have the same properties.[6] It is possible to treat bullous keratopathy with flush-fitting lenses, but in our experience, the use of such lenses requires complicated and laborious fitting techniques and results in less predictable visual improvement. More important, they represent a significant hazard in that if they rotate or become displaced in any way, serious corneal ulceration can result. Our experience suggests that bandage-lens therapy is much easier and safer than either the molded methacrylate lenses or the epikeratoprostheses. In our clinic we try the bandage lenses in virtually every patient with bullous keratopathy. In cases where the degree of visual acuity is not sufficient for the patient's needs, the lenses are removed and a penetrating keratoplasty performed.

## Summary

Bandage lenses were used to treat 49 patients with varying degrees of bullous keratopathy and proved successful in 41. These cases have been followed from two to 24 months. In eight cases, the lenses were discontinued because of failure to improve vision to a reasonable level in patients who had no significant discomfort. The remaining patients continue to wear their lenses in comfort with significantly improved vision. One corneal ulcer developed, but responded well to treatment and no loss of vision occurred.

Bandage-lens therapy shows considerable promise as a simple, effective method for the treatment of bullous keratopathy. The type of lens and the availability of a variety of powers, radii of curvature, and diameters, are important for optimal visual acuity, as is meticulous refitting after an initial period of adjustment.

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# MICROCYSTIC DYSTROPHY OF THE CORNEAL EPITHELIUM

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In 1964, Cogan, Donaldson, Kuwabara, and Marshall[1] described a new entity, microcystic dystrophy of the corneal epithelium, characterized by groups of tiny, round or comma-shaped, greyish-white, superficial corneal opacities in the pupillary zones of both eyes. Histologic studies showed intraepithelial cysts containing keratinized debris and extensions of the basement membrane forming an anomalous membrane within the epithelial layer of the cornea. All of the five reported patients were healthy adult women, with negative family histories. The corneal opacities disappeared without leaving scars, and over the years other opacities appeared. Although a temporary reduction in visual acuity and mild irritation was occasionally noted, most patients were free of complaints.

In 1965, Guerry[2] reported seven cases which conformed to the clinical and histologic findings of Cogan and his associates. Of the seven, two were males. In addition to the typical corneal opacities, Guerry observed in every case a maplike dystrophy over the entire corneal surface as a constant clinical sign (Fig. 1). Guerry added that cataract extraction can be performed in these cases without disturbance to the cornea.

In 1966, Wolter and Fralich[3] reported still another case that confirmed the clinical and histologic observation of Cogan and his group and it was their belief that the origin of the cysts was from the basal epithelium.

The two cases which are now reported show both the characteristic corneal opacities of Cogan and associates, and the maplike opacification of Guerry.

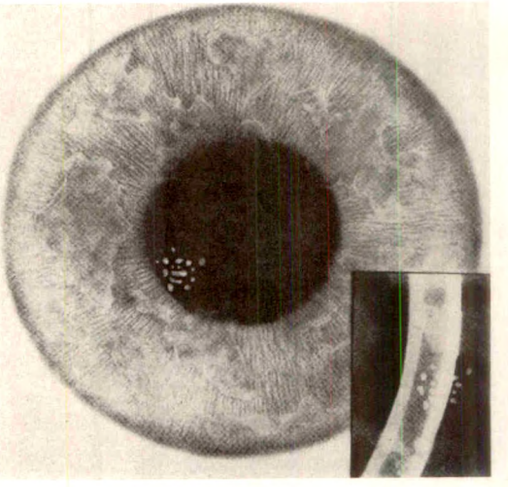


Fig. 1 (Levitt). Artist's composite drawing of two lesions on biomicroscopy: Cluster of superficial corneal opacities (cysts), easily seen, and diffuse maplike opacification visible only in oblique illumination (courtesy of D. Guerry III).

## CASE REPORTS

*Case* 1—A white woman, 51 years of age, was first seen in May, 1963, and has been re-examined at intervals to date. She complained of blurred vision of one or the other eye on at least three occasions. Each time, groups of discrete, irregularly-shaped greyish opacities were observed in the pupillary zone, suggesting a peculiar epithelial disturbance that could not be categorized. Each time the corrected visual acuity of the affected eye was reduced to 20/70 or 20/50, and within several months improved to normal, with disappearance of most of the opacities. At no time was the eye inflamed. The corneal sensation, tested with a cotton wisp, was normal. In September, 1965, I first noted a diffuse, lacy film in the epithelium of both eyes of this patient which seemed to become more pronounced with each succeeding examination. Dilatation of the pupil made it easier to discern the opacification. The appearance suggested an oil slick in water (Fig. 2).

In 1960, this patient's left kidney was excised because of a large, palpable tumor which proved to be a renal cell carcinoma. She has enjoyed good health since, and yearly physical examinations and chest x-ray studies are negative. Electrophoresis of blood serum and urine are negative. Family history is non-contributory. In December, 1969, the patient was examined by Dr. Frederick Theodore, who suggested microcystic dystrophy of the corneal epithelium as a possible diagnosis.

At the last examination, in May, 1970, corrected visual acuity was RE: 20/25 with —3.25 sph. ⌒ —0.75 cyl. ax. 135°, and LE: 20/30 with —3.50 sph. ⌒ —0.75 cyl. ax 180°. Only a few scattered white opacities were seen in the corneas, but the diffuse maplike film was very apparent in each eye. She also had incipient peripheral opacities

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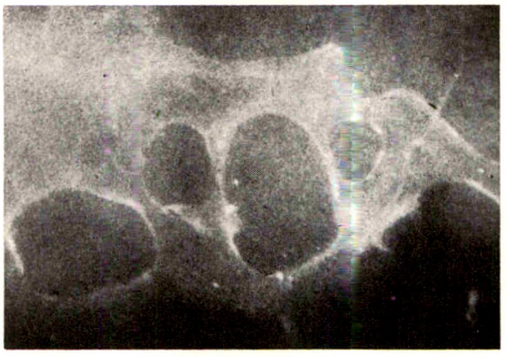


Fig. 2 (Levitt). Slit lamp view of diffuse, maplike changes in the epithelium, resembling an oil slick in water.

of both lenses. The fundi were essentially normal in appearance.

*Case 2*—A white woman, 67 years of age, was examined in December, 1969. She had no complaints. Corrected visual acuity was RE: 20/30 with −1.50 cyl. ax. 45°, and LE: 20/40 with −1.50 cyl. ax. 180°. Both eyes looked grossly normal. On biomicroscopy, clusters of discrete, spherical white opacities were visible in the lower pupillary zones (Fig. 3). These spots could not be seen with the naked eye, but were easily visible with an eight diopter magnification hand loupe. With oblique illumination the same "oil slick in water" opacification was observed in both eyes as in Case 1. In addition, yellowish-green branching lines (Hudson-Stahli) were observed in the corneas.

In 1958, a benign tumor of the colon was excised; the patient has been in good health since. At her last visit, in May, 1970, there were no marked changes in the eye findings.

## Discussion

These two cases present evidence that the maplike dystrophy described by Guerry is part of the syndrome first reported by Cogan and associates.

The evidence so far indicates that microcystic dystrophy of the corneal epithelium is a purely epithelial disturbance. The disease does not extend beyond the basement membrane. Removal of the epithelium is curative, since the newly formed epithelium remains normal.

The two salient findings of superficial white spots and diffuse opacification are quite distinctive and cannot be mistaken for anything else, once one is aware of this entity. For differential diagnosis the reader is referred to a tabulated list compiled by Falls[4] of numerous disease entities involving the corneal epithelium.

## Summary

Microcystic dystrophy of the corneal epithelium is characterized by groups of tiny round or comma-shaped, greyish-white superficial corneal opacities in the pupillary zone of each eye. These findings are described in two patients, one, a 50-year-old white woman, had a transient decrease in vision to 20/70. Vision improved to normal with disappearance of most of the opacities. The second patient, a 67-year-old white woman, had corrected vision of 20/30 and 20/40. Epithelial changes of the cornea were similar to those seen in the first patient and resembled an oil slick on water.

## Acknowledgment

The photographs were taken by Don Wong, R.B.P.

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Fig. 3 (Levitt). Slit lamp view of cluster of whitish opacities in the epithelium.

# CORNEAL THICKNESS DURING CORNEAL HOMOGRAFT REJECTION AND UVEITIS IN RABBITS

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Corneal thickness measurements are valuable in predicting the short-term outcome of penetrating keratoplasties.[1] Changes in thickness result from an interaction between the factors that affect corneal endothelial function. The present study was designed to determine the effects of graft rejection, uveitis and other factors on corneal thickness. The following categories of corneal involvement were studied: (1) normal cornea, (2) uveitis in unoperated eyes (normal), (3) "normal" autografts, (4) uveitis in autografts, (5) "normal" homografts, (6) homografts with skin grafts (second set), and (7) uveitis in homografts.

We wanted to determine if changes in thickness occurred before clinically detectable graft rejection or uveitis and what effect these events had on corneal thickness. The results indicate that pachometry is a useful quantitative tool when used to assess keratoplasty.

## MATERIAL AND METHODS

Adult (2 to 3 kg) albino rabbits of both sexes were used in all experiments. Under intravenous pentobarbital anesthesia, 7 mm penetrating corneal grafts were exchanged between animals (day 0) as previously described.[2] Running 7-0 black silk sutures were used, and operated eyes were treated daily with Neosporin ointment and 1% atropine drops until suture removal (day 10). To induce corneal homograft rejection, abdominal skin grafts were exchanged between the same animals on day 14. In a second group, 7 mm corneal autografts were rotated in situ and sutured with 7-0 black silk.

Uveitis was induced in normal and grafted eyes by an intravitreal injection of 2 ml of egg albumin in 0.1 of sterile saline solution. A 27-gauge needle was used to introduce the albumin into the vitreous.[3] Control animals received intravitreal saline alone.

Animals were examined and corneal thickness measurements made daily by independent observers who were unaware of which animals had homografts and which autografts. An arbitrary scale was established to evaluate changes. The following list of descriptive changes was graded on severity based on a scale of 0.1 to 1: limbal flush, iris rubiosis, cells in the anterior chamber (flare), corneal haze, corneal vascularization, and graft clouding.

The central corneal thickness measurements were made on various days (Table 1), using a modified Haag-Streit pachometer,[4] and at the termination of the experiment, clinical observations and thickness measurements were correlated.

## RESULTS

In the normal cornea, thickness ranged from 0.35 to 0.48 mm, with thin corneas occurring in very small animals. In most of the rabbits, thicknesses ranged between 0.40 and 0.45 mm. Day-to-day variations in thickness were 0.02 mm or less, with the two eyes of each animal never varying by more than 0.01 mm from each other. The correlation of thickness and clinical results are found in Table 1.

*Uveitis in unoperated eyes*—A mild uveitis was induced in one eye of 11 animals (day 0). The course of the uveitis was described previously.[3] The uveitis was apparent by the fifth day in all animals, but corneal thickening did not occur until the sev-

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Reprint rquests to Joseph Capella, M.S., Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, Florida 32601.

TABLE 1

CORRELATION OF THICKNESS AND CLINICAL CHANGES

| Category | Thickness Changes | | | Clinical Changes | |
|---|---|---|---|---|---|
| | Initial Thickness (in mm) | Peak Thickness (in mm) | Day Observed | Clinical Signs | Day Observed |
| Uveitis in unoperated eyes | .422 ± .010 | .485 ± .045 | 7 | Limbul flush, iris rubiniosis, cells in anterior chamber | 5 |
| Autografts | .41 ± .01 | .627 ± .144 | 10 | Corneal haze | 10 |
| Uveitis in autografts | .412 ± .010 | .51 ± .34 | 10* | Limbal flush, iris rubiosis, cells in anterior chamber | 7 |
| Homografts | .41 ± .01 | .60 ± .133 | 10 | Corneal haze | 10 |
| Homografts with skin grafts | .41 ± .01 | — | 14* | Cells in anterior chamber, corneal vascularization, corneal haze, graft clouding | 12 |
| Homografts with uveitis | | | | Cells in anterior chamber, corneal vascularization, corneal haze, graft clouding | 4 |
| Cloudy | .413 ± .011 | .713 ± .20 | 11* | | |
| Clear | .416 ± .020 | .523 ± .023 | 19* | Cells in anterior chamber,† graft clouding corneal vascularization | 4 |

* This time represent days after challenge.
† The degree of clinical signs was not as marked as in those that clouded.

enth day (Fig. 1). Corneas eventually thickened 20% and then returned to near normal thickness as the uveitis subsided (day 15). By the 25th day, corneal thickness was completely normal in all animals and no change in thickness was noted in the fellow eyes (Fig. 1). The clinical signs of uveitis (represented by the shaded area of Fig. 1) appeared earlier than the observable thickening and peaked at the fifth day. There was no change in thickness in animals receiving intravitreal saline.

*Autografts*—Nine animals had successful corneal autografts (Fig. 2). Following surgery, corneal thickness gradually increased until suture removal on day 10. Five animals had peak values on this day and a drop in thickness of 0.16 mm or less after suture removal. By day 20 the average thickness was 0.47 mm and dropped to 0.40 mm one week later. It is obvious that this postoperative changes in thickness in both these autographs and the later homografts are due largely to the wound trauma and possible manipulation of the endothelium. All normal auto- and homografts returned to average normal thickness by day 30.

*Uveitis in autografts*—On day 45, uveitis was induced using intravitreal albumin in four autografted eyes. All developed a mild uveitis with 25% increase in graft thickness (Fig. 3). Thickness increases were maintained longer than in nongrafted eyes and measurements did not return to normal until day 75. Clinical signs occurred earlier than in normal eyes (shaded area in Fig. 3).

*Normal homografts*—Successful corneal homografts were performed in 20 rabbits, and six of these who did not receive skin grafts did not reject their corneal grafts (Fig. 4). The pattern of change in thickness in the animals without skin grafts was the same as in autografted animals, and by day 20 all had normal thickness.

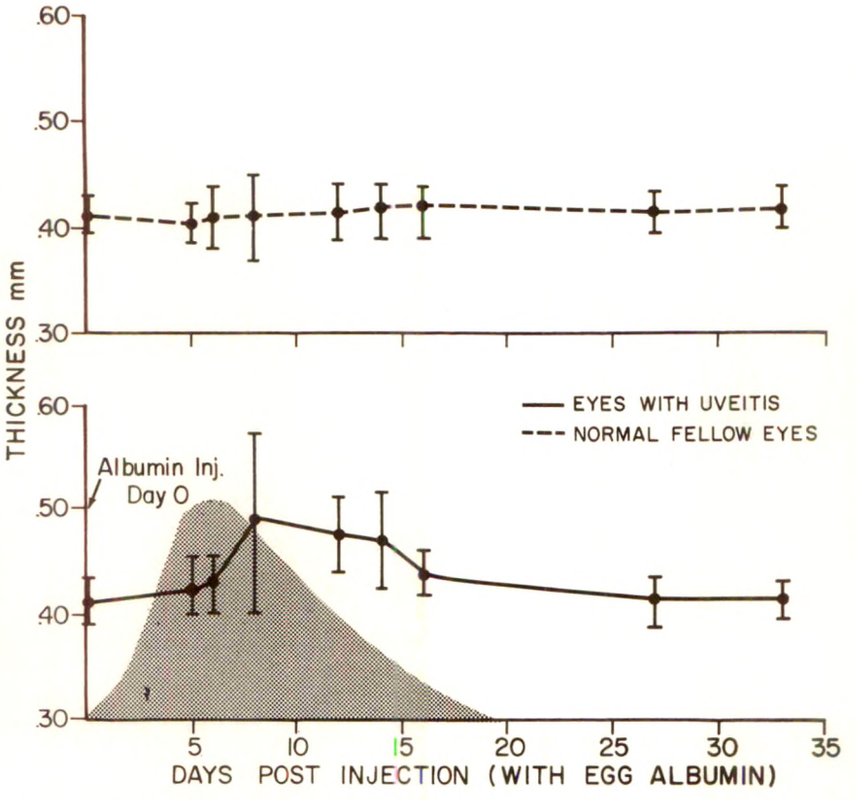



Fig. 1 (Capella and Waltman). Changes in corneal thickness with albumin induced uveitis. Experimental eyes are shown below by solid line, control fellow eyes are shown above with interrupted line. The shaded area in the lower graph represents the appearance of clinical symptoms as described.

*Homografts with skin grafts*—Fourteen animals received skin grafts from their corneal donor animals on day 14. On day 20, all had clear corneal grafts, and while the mean corneal thickness of the grafted eyes was slightly greater than the other groups, it was only 10% higher (0.49 vs 0.45 mm) than their untreated control eye (Fig. 5). This thickness difference between groups was due in part to the use of larger animals. Homograft rejections began 12 days after skin grafting (day 26). A limbal flush with dilatation of iris vessels and engorgement of corneal vessels leading to the graft occurred.[2] A fine line of keratic precipitates appeared on the peripheral graft endothelium and then progressed centrally. No changes in corneal thickness occurred until two days following clinical signs of rejection (approximately day 28) (shaded area of Fig. 5) Definite evidence of rejection was always present at least 24 hours prior to thickness changes.

*Uveitis in homografts*—Approximately 25 days after keratoplasty, six animals received intravitreal albumin injections (Fig. 6). Within one week, a 25% increase in thickness was noted in all animals. Three animals maintained this increased thickness for four weeks, and then their corneas gradually thinned to near normal levels at two months. The other three had a continued rapid increase in thickness to 0.90 mm during the fifth week and their grafts became clouded.

When clinical rejection was first observed, both eyes of six additional homografted animals were treated for 10 days with 0.1% dexamethasone drops twice daily. In grafted eyes, the rejection phenomenon regressed

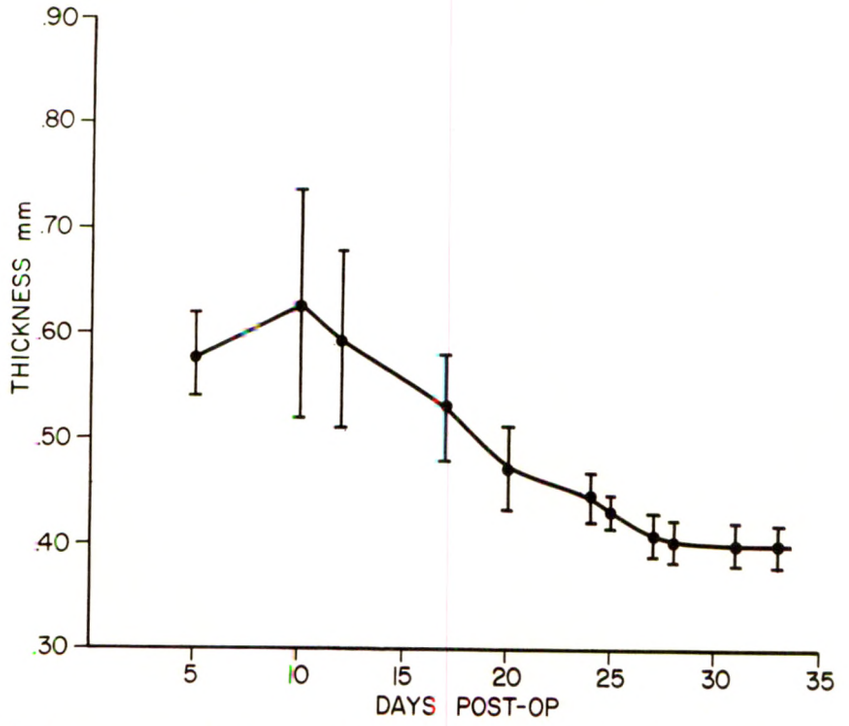



Fig. 2 (Capella and Waltman). Postoperative corneal thickness of full-thickness corneal autograft. The 95% confidence intervals are shown.

and there was no change in corneal thickness. When the corticosteroids were discontinued, corneal thicknesses increased and rejection occurred. In the six nongrafted eyes, no change in corneal thickness was noted during or after corticosteroid therapy.

## Discussion

Corneal thickness is a useful clinical parameter for predicting the prognosis of donor tissue following penetrating keratoplasty.[1] In clinical studies, however, the considerable variation in both donor material

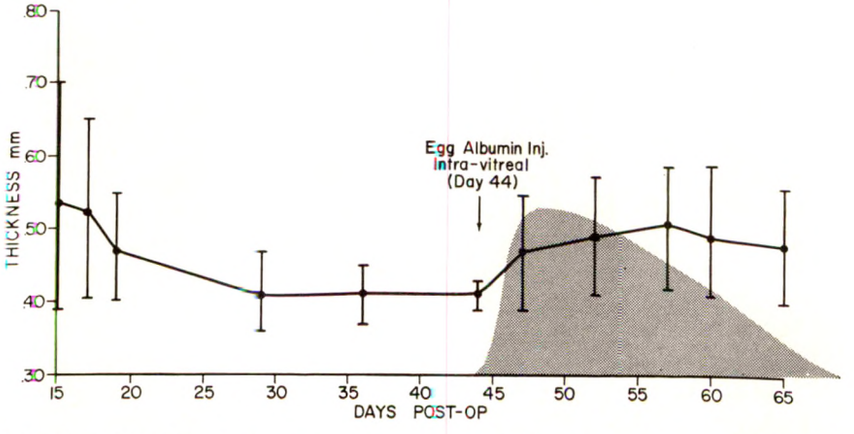



Fig. 3 (Capella and Waltman). Corneal thickness after uveitis in corneal autografts. The shaded area represents the arbitrary value placed on the clinical signs as they appeared before obvious thickness.

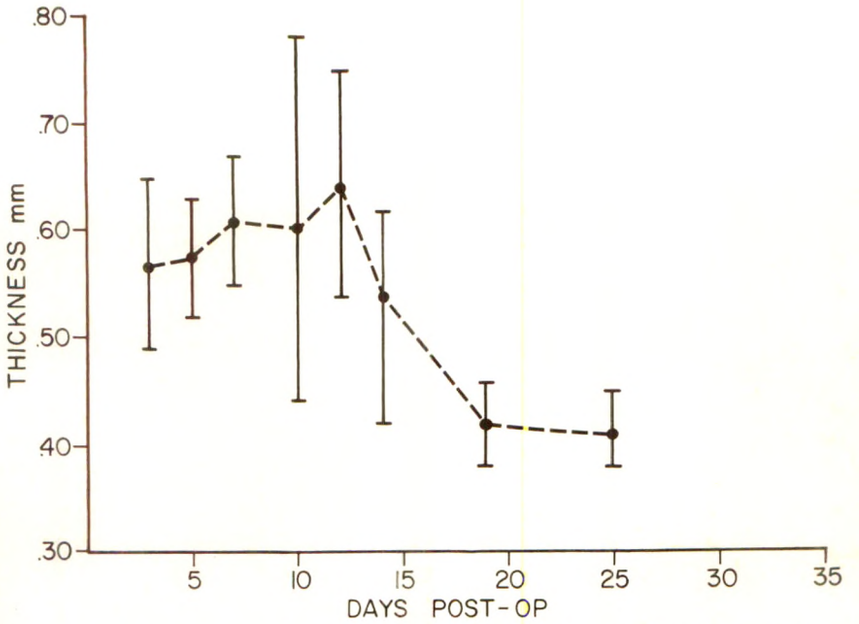



Fig. 4 (Capella and Waltman). Postoperative corneal thickness in nonrejecting normal corneal homografts.

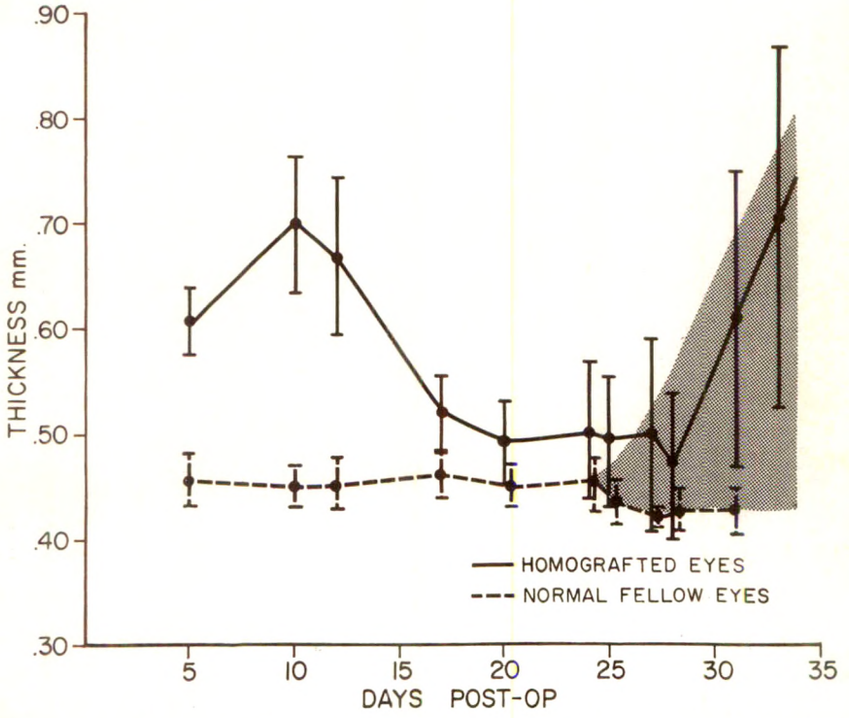



Fig. 5 (Capella and Waltman). Corneal thickness changes induced by a skin graft (second set) in corneal homografts. The grafted eyes are depicted by a solid line, the fellow, unoperated eyes by the interrupted line. The shaded area represents the onset of clinical signs in advance of observable thickness changes.

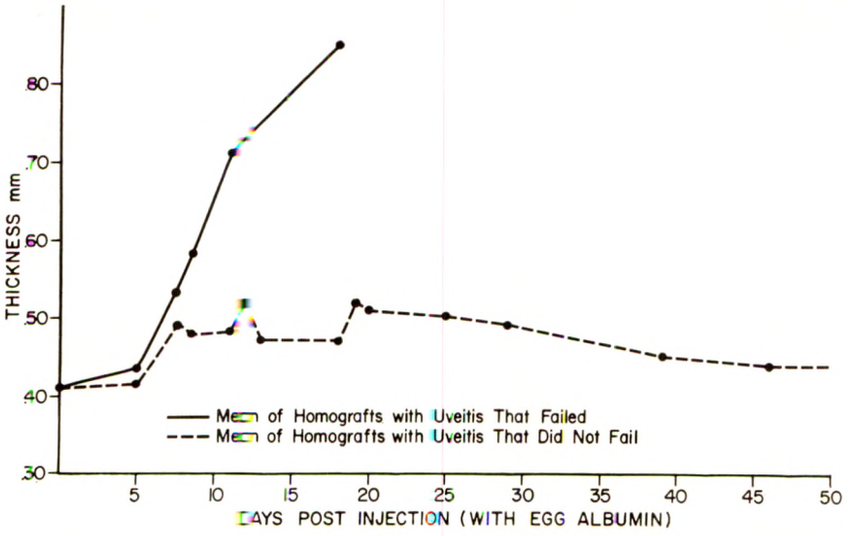



Fig. 6 (Capella and Waltman). Corneal thickness in homografted eyes with induced uveitis; 50% rejected to the point of opacification (solid line, and 50% recurred with apparently little alterations in clarity.

and postoperative course make it difficult to evaluate the influence of other factors on endothelial function and thickness. In this regard, several interesting observations have arisen from our studies.

The pattern of corneal detumescence and resumption of normal thickness in rabbits after keratoplasty was similar in corneal autografts and nonrejecting homografts. Maximal thickness was reached just before or just after suture removal. Thin grafts became temporarily thicker and thick grafts thinned following suture removal, suggesting that mechanical factors affecting endothelial alignment are important. In thick grafts, less than optimal suture placement may prevent defects between donor and host endothelium from closing until after suture removal. In thin grafts, the trauma of suture removal may cause a temporary disturbance of endothelial function. Within 10 days after suture removal, however, all grafts returned to normal thickness.

The increase in thickness during the first 10 postoperative days is undoubtedly due in part to surgical trauma and postoperative uveitis. In otherwise normal eyes, induced mild uveitis caused a 20% increase in corneal thickness. In all cases, the uveitis was clinically detectable at least 24 to 48 hours prior to changes in thickness, although no quantitative value could be put on the degree of corneal involvement. Previous studies revealed that endothelial damage occurred in uveitis and led to increased thickness.[5] Logically, the anterior chamber flare was evident before changes in thickness. These eyes regained normal thickness in about two and one-half weeks. Uveitis in well-healed autografts created a 25% increase in thickness with a prolonged recovery period of one month. The only obvious reason for this prolongation is the trauma induced by the surgery. Homografts also thickened by 25% following uveitis and recovery was delayed for two months in those grafts that did not cloud. This is most likely due to the increased loss of endothelium brought about by the uveitis. Fifty percent of the homografts with uveitis clouded and doubled in thickness and by day 10 it was possible to predict which homografts would eventually recover. It is safe to assume that the clouded homografts lost the entire endothelial sheet due to some immunologic process resulting in their immediate clouding. The remaining 50% that cleared

possibly had some immunologic tolerance and therefore were able to recover.

In second-set rejecting homografts, thickness reached a minimum at day 21 and stayed there for an additional week. There were no definite signs of rejection by thickness changes prior to obvious clinical signs. Rejection could be reversed and thickness changes prevented if corticosteroids were given prior to an increase in thickness. However, once there was sufficient endothelial damage to cause central corneal swelling, topical corticosteroids could not reverse the rejection process. In our animals, corneal thickness usually doubled and the entire endothelium and graft were rejected within 48 hours. In more smoldering rejections, where endothelial damage and thickness changes are more gradual, the use of immunosuppressive agents may allow for recovery. Finally, it is noteworthy that the untouched normal fellow eyes of all our animals were not affected by graft rejection, uveitis, or therapy in the experimental eye.

The alterations in thickness in these various categories studied are unquestionably linked to those clinical parameters described previously. However, the use of thickness measurements as an index of the degree of corneal involvement can and has proven to be a significant factor in post-keratoplasty follow-up.

## Summary

Corneal thickness was measured following penetrating corneal autografts and homografts and induced uveitis in rabbits. Normal grafted tissue regained normal thickness approximately three weeks after surgery. Thickness increased rapidly during homograft rejection, but not until rejection was clinically apparent. Topical corticosteroids could reverse the rejection process if instituted prior to thickness changes.

Albumin induced uveitis caused a 20 to 25% increase in thickness in both normal and grafted eyes. Uveitis was easily detected prior to changes in corneal thickness. After uveitis induction, nongrafted corneas regained normal thickness in two and one-half weeks, while autografts required a month and homografts two months. Fifty percent of the homografts became opaque after induced uveitis and by pachometry were apparent by the 10th day after uveitis induction.

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# INTEGRITY AND POSITION OF THE ANTERIOR HYALOID MEMBRANE FOLLOWING CATARACT EXTRACTION

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Observations of the hyaloid membrane, made over a period of years following surgical extraction of the crystalline lens, reveal that in some eyes the integrity and location of this membrane seem totally unaffected. In a significant number of eyes, however, the membrane may show changes that probably result from the surgical procedure itself, from absence of the lens as a supporting structure, or from other as yet undefined causes.

This study reports the frequency of various observed changes in the hyaloid membrane after intracapsular cataract extraction. A few observations were made on eyes in which cataracts had been removed by the extracapsular method.

## MATERIALS AND METHODS

Data were obtained on 75 eyes in 56 patients examined over a period of about five years. All eyes were operated on by the same surgeon (G.P.L.). The surgical procedure for 69 of the eyes was intracapsular cataract extraction with some variation in the types of iridectomy performed. The remaining six cataracts were extracted extracapsularly.

Observations were begun approximately one month following the operation; during the first year, subsequent observations were spaced three months apart. Thereafter, an attempt was made to space the observations at four-month intervals.

At each examination, the hyaloid membrane was inspected with a slit lamp for discontinuities or breaks in its structure. Moreover, data obtained with a Zeiss anterior chamber depth micrometer was used to calculate relative protrusion of the membrane into the anterior chamber. Relative protrusion, or prolapse, is defined as the amount (in percent of anterior chamber depth) the axial part of the hyaloid membrane moves toward the cornea. Prolapse (%P) is calculated as follows: $\%P = ACD-VL/ACD \times 100$, where ACD is anterior chamber depth, and VL is vitreous location, i.e., distance from the axial part of the hyaloid membrane to the posterior corneal surface. For example, a vitreous location of 3 mm in an anterior chamber 4 mm deep yields a vitreous prolapse of 25%.

In most of the observed eyes, it was evident that the anterior hyaloid membrane was not rigidly fixed in position, so a membrane appearing to have a certain location relative to the iris plane at one moment might show a measurable change of position on subsequent measurement. Before analyzing the data, therefore, it had to be decided how large a vitreous protrusion would be considered significant. Examination of data from successive observations led to the decision that an apparent vitreous prolapse of less than 10% is not significant. Thus, in a given case, variation of the extent of vitreous prolapse would be significant only if it exceeded 10% (±) when compared with mean values obtained earlier. We recognize that, in a given instance, factors other than chance movement of the vitreous contribute to the variability of the prolapse extent. Two of these factors are uncontrolled changes of position of the observed eye and inherent errors in the measuring procedure. The accu-

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racy of the measuring procedure, which utilizes the Zeiss anterior chamber depth micrometer, has been discussed elsewhere.[1]

## Results

The findings revealed several distinct groups: In Group 1, the 53 eyes of this group all had intact anterior hyaloid membranes during the five year study. Among these eyes, however, there were the following subgroups: (A) Fairly constant vitreous prolapse existed for 24 eyes, 13 of which had an average prolapse of 37%, ± 10, while 11 had essentially zero prolapse throughout the five years. (B) Vitreous prolapse decreased with postoperative time in 29 eyes. Prolapse decreased gradually for 22 of these eyes from an initial value of 53%, ±22, to a final mean value of 22%, ±14, at an average rate of 5.8%, ±4.7, per year. In the remaining seven eyes of this subgroup, prolapse decreased less linearly than in the other 22, and approached zero after four or five years following an initial value of 29%, ±14.

In Group 2, the anterior hyaloid membrane in these 16 eyes was either lacking entirely at first examination (12 eyes), or lost its integrity within two and one-half to three years, exhibiting one or more holes or disappearing entirely (four eyes). In Group 3, because extracapsular extraction was employed on the six eyes of this group, it is in a different class from the preceding ones. Measurements on these eyes pertained to location of the lens capsule remnant and not to hyaloid membrane location. As would be expected, the anterior surface of the lens capsule showed no significant protrusion into the anterior chamber over the five years. In fact, the average long-term location of the anterior capsule surface tended to be slightly behind the iris plane (negative prolapse) with extreme values of + 11% and − 25% at specific times during the five years.

## Discussion

In Group 1-B, the significant prolapse reduction observed over a period of years is supported by the findings of Goswami and associates[2] who believe the vitreous body shrinks in the course of time. This view, however, is open to question because the observed prolapse decrease could be explained just as easily by a movement of the entire vitreous body toward the retina after a prior detachment from the posterior fundus. In line with this reasoning, the unchanging but significant vitreous hernia found in 13 eyes of Group 1-A could be explained by the occurrence of a detached vitreous after the operation and by failure of the vitreous to move backward. Obviously, this matter can be settled only by future observations of the posterior vitreous soon after the operation and for a period of years thereafter.

Results of the present study point to the following possibilities after intracapsular cataract extraction: (1) the hyaloid membrane may protrude more than a third of the way into the anterior chamber and remain there for several years with no rupture of the membrane. (2) The membrane may protrude at least halfway into the chamber, then gradually recede to about one quarter of the distance from iris to cornea, remaining intact for an indefinite time. (3). The membrane may prolapse significantly to about a third of the anterior chamber depth, then recede to the iris plane in four or five years and remain intact indefinitely. (4) Herniation may be small immediately postoperatively, become negligible in a few months, and show no change thereafter. (5) Finally, at the time of or soon after the operation, the membrane may disappear—an occurrence more likely to be associated with rupture of the hyaloid membrane, either at the time of operation or within the following month. (6) In a few instances, the membrane may remain intact for as long as three years after the operation, followed by a late rupture or a disappearance of the membrane.

With regard to the special category (Group 3) in which extracapsular extraction was performed, results suggest—even though the sample size was small—that the

lens capsule remnant retains its firmness over a period of years following the operation. If significant loss of capsule rigidity had occurred, it would have shown up as a gradual protrusion of the capsule surface into the anterior chamber during this five-year study.

## Summary

A five-year study of 69 aphakic eyes, operated on intracapsularly, showed 53 eyes with intact anterior hyaloid membranes throughout the entire period of study. In 16 others the membrane ruptured or disappeared during the five years. Six additional eyes, operated on extracapsularly, showed no change in location of the lens capsule remnant.

Among the 53 eyes with intact membranes, 24 showed fairly constant vitreous prolapse over the test period. Thirteen of these had an average prolapse of 37%, ±10, and 11 had nearly zero prolapse. In the 29 eyes with changing prolapse, 22 were characterized by gradual reduction from 53%, ±22, to 22%, ±14, at an average rate of 5.8%, ±4.7, per year. The remaining seven eyes of this group had almost zero prolapse at the end of four or five years after a postoperative value of 29%, ±14.

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## Ophthalmic miniature

"I am half distracted, Captain Shandy," said Mrs. Wadman, holding up her cambric handkerchief to her left eye, as she approached the door of my Uncle Toby's sentry box, "a mote—or sand—or something—I know not what, has got into this eye of mine. Do look into it—it is not in the white—"

In saying which, Mrs. Wadman edged herself close in beside my Uncle Toby, and squeezing herself down upon the corner of his bench, she gave him an opportunity of doing it without rising up. "Do look into it" said she.

"I protest, Madam," said my Uncle Toby, "I can see nothing whatever in your eye."

"It is not in the white," said Mrs. Wadman. My Uncle Toby looked with might and main into the pupil.

Lawrence Sterne
*Tristram Shandy*, 1760

# LASER IRIDECTOMIES

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In 1956, Meyer-Schwickerath[1] described the use of a xenon arc photocoagulator to produce iridectomies. He reported a high incidence of corneal and lenticular opacities and recommended that this procedure be performed only in aphakic eyes. In 1958, McDonald and Light[2] used copper-covered carbon arcs as a source of high intensity light for the same purpose, but they, too, found that they had produced corneal and lenticular opacities. Similar undesirable burns were described by Hogan and Schwartz[3] in 1960, and by Burns[4] in 1965.

The probable cause of lenticular and corneal burns during photocoagulation of the iris is the heat conducted from the surface of the photocoagulated iris. The longer the time required to perform the iridectomy, the greater the burn to the adjacent tissues. Iridectomy with a xenon are photocoagulator requires an exposure of several seconds. It was hoped that with a laser, which produces large amounts of energy in a shorter time, iridectomies could be produced without damage to lens or cornea.

In 1964, Flock and Zweng[5] reported their inability to create iridectomies using a 0.1 joule ruby laser. In 1967, Snyder,[6] using a 0.3 joule ruby laser on the iris of Dutch Chinchilla rabbits, could not produce a penetrating hole with a single burst. He did succeed in penetrating the iris with multiple bursts of laser energy on the same target and described late hole formation in the iris at the site of a single burst as a result of iris atrophy. He observed that retinal burns occurred in a large number of eyes on which multiple laser bursts were used to produce an iridectomy. No lenticular or corneal opacities were noted. Campbell and co-workers[7] used a focused neodymium laser beam of up to 8 joules and reported the creation of severe burns of the iris without hole formation, but with corneal and lenticular opacities. Zweng and his associates[8] recently reported the successful creation of iridectomies in brown eyed rabbits using a single burst of ruby laser energy. The results with approximately equal amounts of energy were for some reason, not consistent. Iridectomies were also created in monkey irises using long-pulsed and Q-switched ruby energy. These iridectomies closed off and either opened by atrophy or were reopened by additional bursts of energy. Holes were created in brown irises using repeated applications of argon laser energy. Iridectomies could not be created in blue or light brown irises.

To study the factors producing iridectomy in rabbit iris using a single burst of laser energy, a laser with interchangeable ruby and neodymium rods was used.

## MATERIALS AND METHODS

*Laser equipment*—A biomedical laser system consisting of a solid-state laser head with interchangeable ruby and neodymium rods is used. The laser head is joined to a modified Zeiss operating microscope (Fig. 1). Binocular viewing through the microscope is along the line of the laser beam (Fig. 2). At the time the laser is fired, a shutter swings across the viewing system, completes the firing circuit, and triggers the laser (Fig. 2). The shutter protects the operator's eyes from possible reflections of the laser beam.

*Application*—The amount of energy di-

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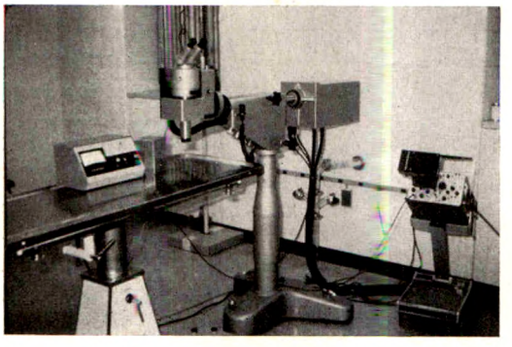


Fig. 1 (Beckman and associates). Laser combined with a Zeiss operation microscope.

rected at the iris is controlled by varying three factors: (1) the laser energy is increased directly and linearly with the amount of voltage used to excite the xenon flash lamps; (2) the amount of energy is increased directly and linearly by increasing the number of capacitor and inductor banks used (i.e., with three banks the pulse lasted 3.0 msec, and with six banks, 6.0 msec); (3) the laser beam was passed through one of eight apertures, decreasing in width from ½ to 1/16 inch in 1/16-inch steps. The energy directed at the iris decreased directly and linearly as the width of the aperture chosen diminished in size. Varying combinations of voltage, capacitor banks and apertures were used in iridectomy attempts.

Over 300 iridectomy attempts were performed, both on enucleated rabbit eyes, and on the eyes of living albino and brown-eyed rabbits. When live animals were used, they were anesthetized with an intravenous injection of sodium nembutal.

High-speed color cinematography, using a Hycam camera (400-10,000 frames per second) and 16 mm Kodak Ektachrome EF film, was employed to record iridectomy formation.

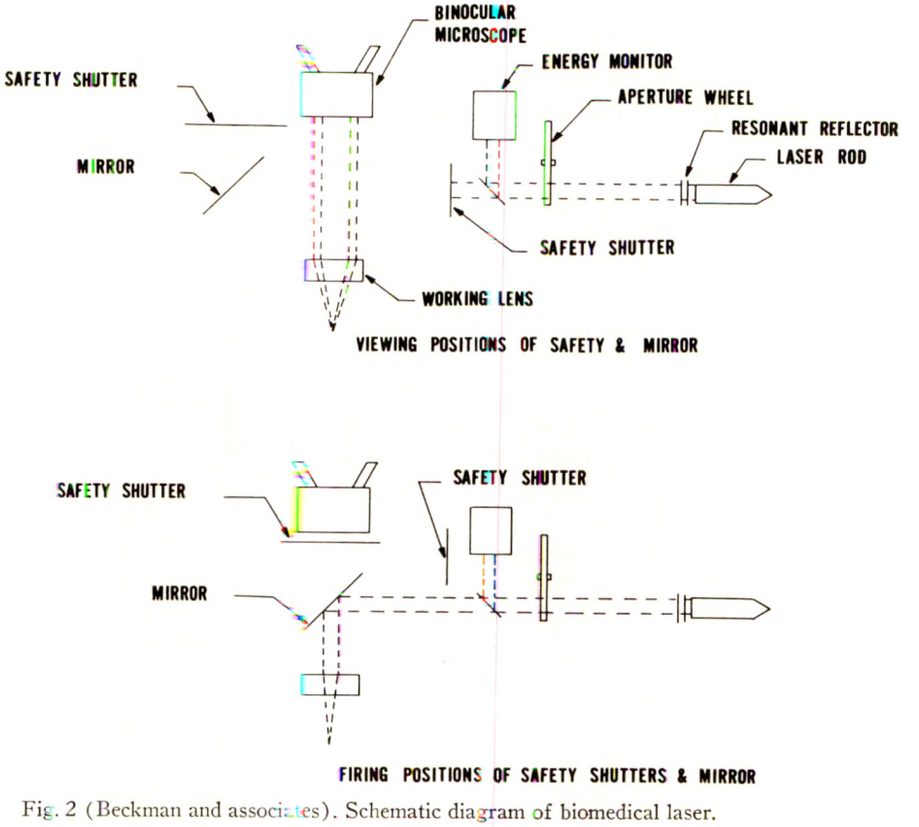



Fig. 2 (Beckman and associates). Schematic diagram of biomedical laser.

## Results

### Energy factors

When the number of capacitor and inductor banks used remain constant, any combination of aperture size and voltage sufficient to allow iridectomy threshold energy to become incident on the iris will result in a penetrating iridectomy. On brown irises this was found to be 3.2 joules for ruby, and 3.8 joules for neodymium laser energy. On albino irises it was found to be 12 joules for ruby energy. No iridectomies could be created in albino irises using neodymium energy.

When the number of capacitor and inductor banks was varied while maintaining constant energy levels on the iris, 6.0 msec bursts were found to be much more efficient in creating iridectomies than bursts of shorter duration.

### The distribution of laser energy and its absorption by iris pigment

The lesions produced on a brown iris could be divided morphologically into three zones (Fig. 3). When super-threshold iridectomy energy levels are used, the central zone is a hole through the iris. We refer to this as the vaporized zone. It measures approximately 0.4 mm in diameter regardless of the aperture used. The hole is surrounded by a light grey crater wall ring 0.3 mm wide —the subvaporization zone. The width of the subvaporization zone does not vary with the size of the aperture used. Surrounding the two central zones is a large variable ring of hyperpigmented burned iris tissue—the charred zone. It varies in size directly with the width of the aperture through which the laser beam passes. Typically, the hyperpigmented ring is 1.1 mm wide using a 3/16th inch aperture, and 1.4 mm wide using a 1/4 inch aperture.

All iridectomies produced with ruby energy in brown irises are temporarily closed by stromal fragments and pigment-laden macrophages, two weeks postoperatively.

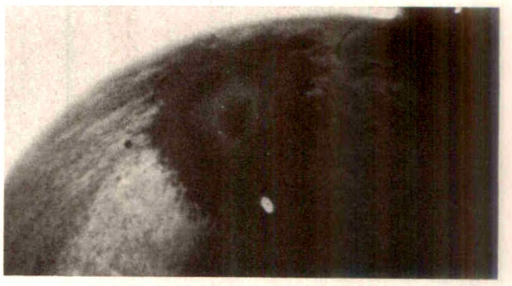


Fig. 3 (Beckman and associates). A ruby laser iridectomy in a brown iris demonstrating the central vaporized hole, the surrounding grey subvaporized crater area and the large hyperpigmented burned zone.

However, a week later, an iridectomy results after atrophy.

When the neodymium laser is used on a brown iris, a 0.3 mm vaporized area is formed (Fig. 4). No visible subvaporization zone is seen and the hyperpigmented burned areas are one-half the size of those created with ruby energy and the same aperture. The majority of these iridectomies remain open.

When albino irises are irradiated with ruby energy, no subvaporization or charred area is seen—only a hole (Fig. 5). All of these iridectomies remain open.

When albino irises are irradiated with neodymium energy, no hole is produced. A subvaporization area is seen since the iris is incompletely penetrated, and no charred area is found.

In attempts to enhance absorption of both ruby and neodymium energy, solutions of 5% fluorescein or Cardiogreen were given intravenously to albino rabbits. Cardiogreen absorbs much more neodymium and ruby energy than does fluorescein. Larger holes were produced in albino rabbits (Fig. 5) with the ruby laser when fluorescein was used. No subvaporization or hyperpigmented zones were seen. When albino rabbits were injected with Cardiogreen and ruby energy was focused on the iris, larger holes were created than without the colorifacient, and subvaporization and hyperpigmented charred zones appeared. When fluorescein was injected and neodymium energy was directed

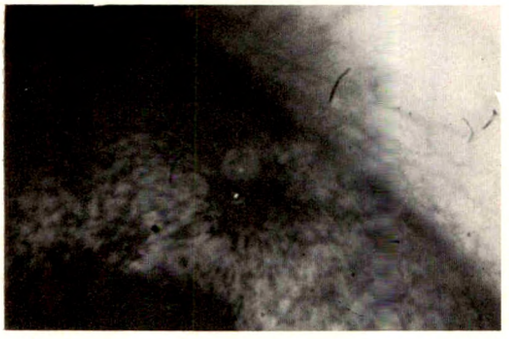


Fig. 4 (Beckman and associates). A neodymium laser iridectomy in a brown iris. Note the full-thickness penetration burn of the cornea and the small area of hyperpigmented burned iris.

into albino irises, no holes could be created but small burns of the iris appeared. When Cardiogreen was injected into albino rabbits, no holes could be created with neodymium energy but very large hyperpigmented burns were found.

Irradiating with either ruby or neodymium energy resulted in massive hyperpigmented burned areas when either fluorescein or Cardiogreen were given to brown-eyed rabbits.

### Transmission of laser energy to the iris through the transparent ocular media

Neodymium energy is absorbed to the extent of 7% by the cornea[7] while almost no ruby energy is absorbed. When vaporization energies are used at the neodymium wavelength, full-thickness burns of the cornea are created (Fig. 5). No such burns occur with ruby energy, but when excessive charring of the iris occurs, endothelial burns result from heating of the aqueous. Laser energy absorption by the cornea does not seem to have a significant effect on the formation of iridectomies.

No lenticular opacities were noted following either ruby or neodymium-created iridectomies.

While keeping energy levels constant, some threshold laser pulses resulted in iridectomies, while others resulted only in burns of the iris. If the target site on the iris was parallel to the axis of the laser rod, the incidence of hole formation was increased, while the incidence of hole formation decreased when the iris target site was perpendicular to the laser rod (Fig. 6). This phenomenon occurred when ruby energy was used, but not with neodymium energy.

*Cooling effect of aqueous*—When the depth of the anterior chamber was decreased by withdrawal of aqueous humor from the eye, iridectomies could be performed in live brown-eyed rabbits using 0.3 joules of ruby or neodymium energy. As the depth of the anterior chamber was increased, increasing amounts of energy were required to create the iridectomies.

In a deep-chambered human eye with a blue iris, about to be enucleated for malignant melanoma, no iridectomy could be created using maximum ruby energy levels. In another blue-eyed patient, with a very shallow anterior chamber due to iris bombe, an iridectomy was created using 7 joules of ruby energy.

High-speed cinematography during the performance of laser iridectomies showed that after the initial vaporization took place, incandescence occurred at the edge of the hole and was much more marked in eyes without aqueous. When aqueous was present, the incandescence was smothered and the hole did not enlarge in size. We feel that aqueous causes a suppressive effect on iris

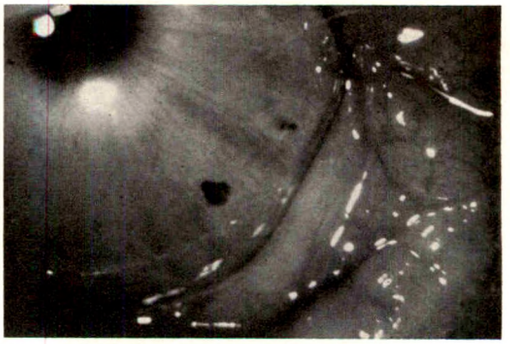


Fig. 5 (Beckman and associates). Ruby laser iridectomies in an albino iris. The laser iridectomy was created using intravenous fluorescein as a colorifacient.

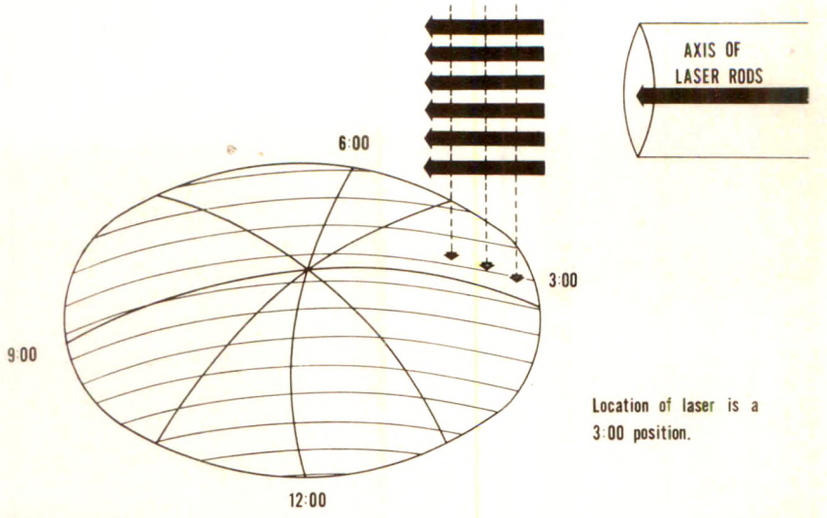



Fig. 6 (Beckman and associates). This shows the relationship between the polarity of the laser rod and the cytomolecular architecture of the cornea.

burns and that the thicker the aqueous layer, the more difficult it is for burning to take place, requiring more energy to create a hole.

*Cooling effect of iris circulation*—A penetrating iridectomy in enucleated brown rabbit eyes required a third less energy than in living eyes. High-speed cinematography showed a shorter period of incandescence at the edge of the hole in living eyes than in the enucleated eyes. This suppression of the incandescence is due to the conduction of heat from the target site by the iris circulation and results in an increased energy requirement for production of iridectomies in live animals.

*Thickness of iris*—If the pupil is dilated, the iris folds upon itself. This presents thicker tissue to penetrate and exposes more surface to the beam. Generally, more energy was found to be necessary to create iridectomies when the pupil was not constricted. With dilated pupils, larger areas of hyperpigmented burns occurred. During our early experiments, miotics were used to control the size of the pupil. Since we felt that this probably contributed to postiridectomy iritis, we later caused miosis by directing a bright beam of light into the eye.

*Length and pigmentation of the eye*—The focal length of the rabbit eye is approximately 8 mm. Since the depth of focus of our laser is 7 mm, it is quite understandable that in over 50% of the eyes in which penetrating ruby laser iridectomies were performed, retinal lesions were found. In all instances, these were white areas approximately 1 disk diameter in size. No retinal hemorrhages were seen. No retinal lesions were found with penetrating neodymium iridectomies, since less neodymium energy is absorbed by the pigment epithelium of the retina and choroid, and more energy absorbed by the lens and vitreous.

## Discussion

We must spectulate as to why 2 and 3 msec pulses were less efficient than longer pulses in forming iridectomies. A laser pulse, although of short duration, is made up of a myriad of much shorter pulses (Fig. 7). We postulate that possibly a "jackhammer" effect is necessary to create the penetration (i.e., the pulse must be of sufficient duration that the energy is available to penetrate the deeper layers of iris tissue after the more superficial layers are vaporized).

The amount of iris charring appears to be directly related to the closing off of the iri-

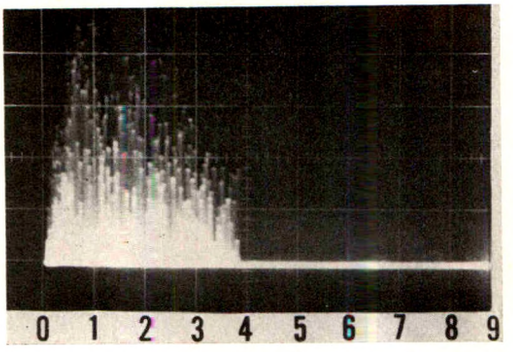



Fig. 7 (Beckman and associates). Oscilloscope recording of laser pulse (scale in msec).

dectomies. We believe this charring is related to the distribution of laser energy onto the target site and the absorption of these energies by the pigment of the iris. To eliminate charring of the iris, all the laser energy should ideally be confined to the vaporization zone. This can be achieved only by *avoiding secondary reflections* of laser energy. We have been able to create iris lesions with smaller hyperpigmented charred zones by locating additional apertures within the laser system at varying points (Fig. 8). We have studied four other possible reasons for aberrant energy falling on the iris outside the vaporization zone with resultant charring:

1. *Focus of the laser beam*—The laser is designed so that the focus of the beam is parfocal with the viewing optics. The depth of focus of the laser beam is 7 mm. Using the 16-power objective of the Zeiss microscope, the depth of focus of the viewing system is more critical than that of the laser beam. For practical purposes, whenever the target site is in focus, the laser beam is also in focus and the minor variations in focusing *would not* account for variations in the size of the lesion produced on the iris or changes in the morphology of these lesions.

2. *Spherical aberration by the delivery lens system*—The lens analysis is shown in Figure 9. The vertical scale represents half apertures. It should be noted that at a $\frac{7}{16}$-inch aperture and smaller, the lens system is diffraction-limited. The magnitude of spherical aberration at a $\frac{7}{16}$-inch aperature is only 0.0076

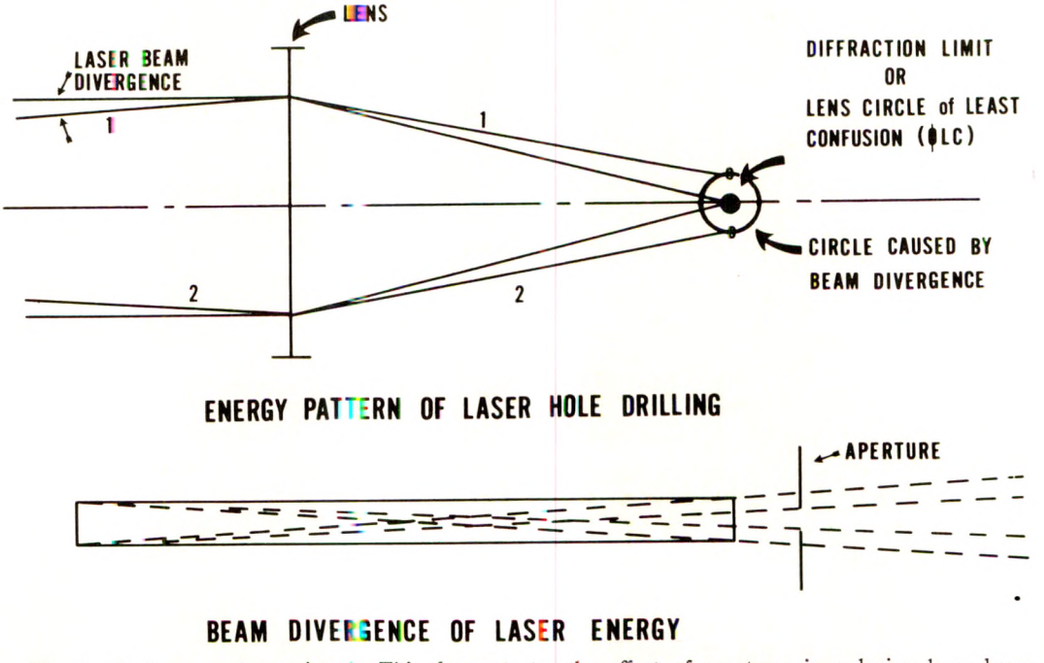



Fig. 8 (Beckman and associates). This demonstrates the effect of apertures in reducing laser beam divergence. It also demonstrates that the circle of laser energy created by laser beam divergence is larger than the circle of least confusion caused by the spherical aberration of the delivery lens.

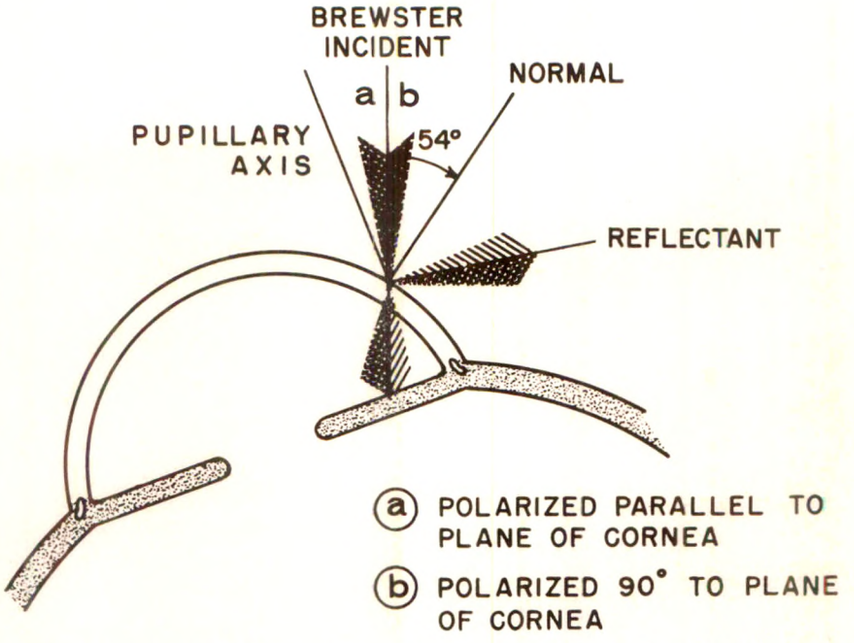



Fig. 11 (Beckman and associates). The rays polarized parallel to the plane of the cornea are better transmitted through the cornea onto the iris at Brewster angle (this angle calculated to be 54° for anterior surface of cornea). The rays polarized 90° to the plane of the cornea are less transmitted and more reflected by the surface of the cornea. (Ruby laser.)

Experimental evidence supports this theory, as shown by Figure 12. Identical energy was used for all four iridectomy attempts in this experiment. The two holes on the left were near Brewster's angle, and the two burns on the right were not. When threshold laser energy is focused on the iris near Brewster's angle, iridectomies are created with ease. On the other hand, when the laser energy incident on the cornea deviates from Brewster's angle significantly, no iridectomies can be created. A shift in the aiming angle towards an angle perpendicular to the iris plane allows less transmission than does an equal deviation towards a horizontal angle (Fig. 10).

The cytomolecular architecture of the cornea seems to result in a polarizing effect in which two axes are represented as geometric opposites in relation to the plane-polarized ruby laser beam. Along one axis, the corneal hemisphere will act with maximum geometric relation to the laser vector allowing Brewster's angle to have maximum effect; while along the other axis, conditions are minimal for Brewster angle effect. Our ruby laser is polarized in such a plane that the corneal hemisphere running from 3:00 to 9:00 o'clock (parallel to the laser rod) allows the Brewster angle to have its maximal effect. Along the 12:00 to 6:00 o'clock axis of the cornea (perpendicular to the laser rod) this effect is minimized (Fig. 6).

## Summary

A laser with interchangeable ruby and neodymium rods was fired through a modified Zeiss operating microscope to study the creation of iridectomies in brown-eyed and albino rabbits.

A pulse duration of 6.0 msec was more efficient in causing the formation of penetrating iridectomies than were shorter pulses. Any combination of voltage input and beam aperture sufficient to give threshold energies of 3.2 joules for ruby laser, and 3.8 joules

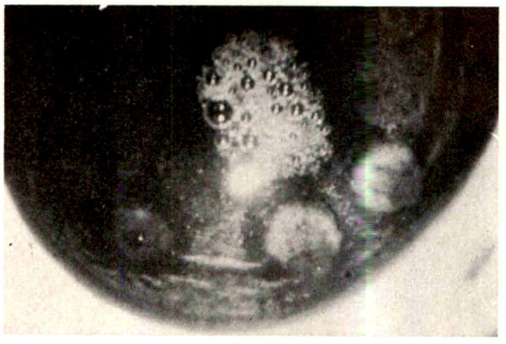


Fig. 12 (Beckman and associates). This demonstrates four attempts at iridectomy formation using identical energy levels. The two penetrating iridectomies on the left were made at Brewster angle while the two incomplete iridectomies on the right were created under identical conditions, except that the laser beam was aimed perpendicularly to the plane of the iris.

for neodymium on brown irises was sufficient for penetrating iridectomy. Ruby energy of 12 joules was required to create penetrating iridectomies in albino irises. No iridectomies could be produced in albino irises using neodymium energy. The iridectomies created in brown irises contain three zones: the vaporized zone, the light grey subvaporized crater, and the hyperpigmented charred zone.

The degree of charring appears to be directly related to the incidence of iridectomy closure. The charring can be decreased by eliminating secondary reflections of laser energy within the delivery system.

Ruby energy is more readily absorbed by iris pigment than is neodymium. Ruby energy would appear to be more optimal for less pigmented eyes since it is better absorbed while neodymium is more satisfactory for brown eyes because charring from aberrant rays of energy is reduced.

Colorifacients enhance absorption of these laser energies.

Ruby wavelength is less absorbed by the ocular media than neodymium energy. Corneal entry burns occurred when neodymium energy was used at iridectomy threshold levels, but not with ruby energy.

No lenticular opacities were noted with either laser source.

Polarized ruby energy is best transmitted through the cornea when its incident angle to the cornea approximates 54 degrees (Brewster's angle) to the normal. No such optimal angle is found for neodymium, since the non-crystalline neodymium rod does not emit plane polarized radiation.

The greater the depth of aqueous overlying the iris, the greater the laser energy required to produce a penetrating iridectomy.

### Acknowledgments

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room, a large space divided by portable partitions to accommodate postoperative patients (Fig. 2).[2] Adult postoperative patients remain on the surgical stretcher, protected by side rails, while infants and children are transferred to cribs in the recovery room. All positions adjoin sources of oxygen and suction; monitoring and emergency equipment are available; and a station for specially-trained recovery room personnel is provided.

Observation galleries in the outer support zone overlook two especially equipped ophthalmic operating rooms (Fig. 3). Admission is regulated at the control desk, but observers in street attire may view surgery without entering the inner operating room zone. A curved wall of tempered glass plate between the gallery and the operating room insures soundproofing and provides an unobstructed view.

The observation of surgery is greatly aided by closed circuit, high resolution television (Figs. 4).[11] One television camera is mounted above the surgical field on the Zeiss twin lamp, and a second camera is incorporated into the optical system of the surgical microscope (Fig. 5). Images on both cameras are viewed on small monitors by surgical personnel, displayed simultaneously on a 21-inch screen in the operating room and on a 14-inch screen in the gallery, and recorded on television tape for future educational use. If desired, the image may be transmitted to other parts of the institute by closed-circuit television.

An audiocommunication system between operating room and gallery, controlled in the surgical area, can permit one-way communication or a two-way conversation. Control of the system insures an uninterrupted concentration on the surgical procedure and prevents any disturbance of a patient under local anesthesia.

*Operating room zone*—Two major operating rooms furnished with equipment especially developed for the Institute occupy the operating room zone (Figs. 4 and 5). Each room is more than 400 square feet in area. Special surgical equipment includes a main column and an auxiliary column suspended from the ceiling and a pedestal anchored to the floor; an equipment cabinet and control console recessed in the side wall are con-

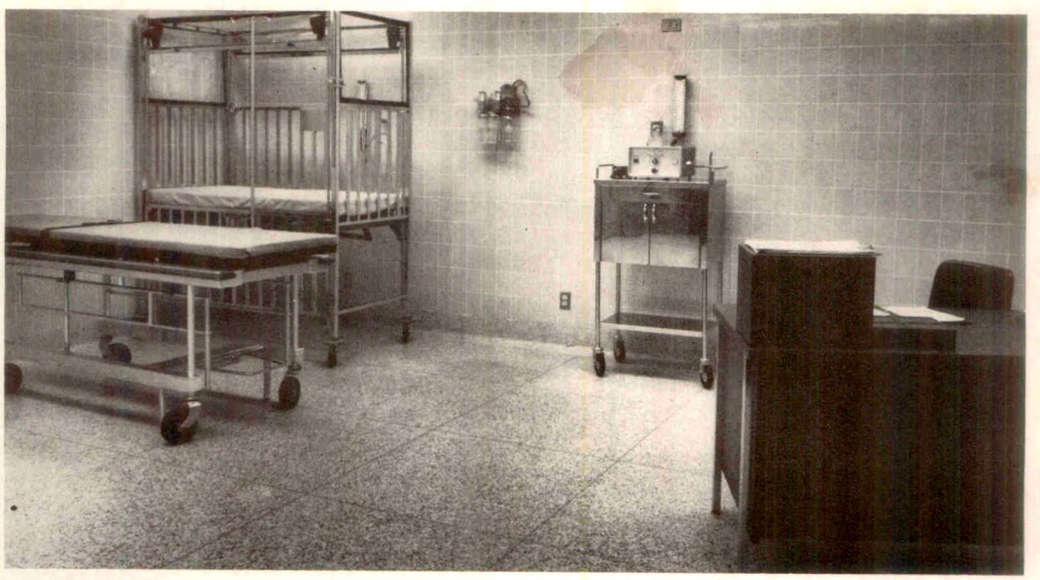


Fig. 2 (Christensen and Straatsma). Recovery room. Adult patients remain on special surgical stretchers; children are transferred to completely enclosed stainless steel cribs.

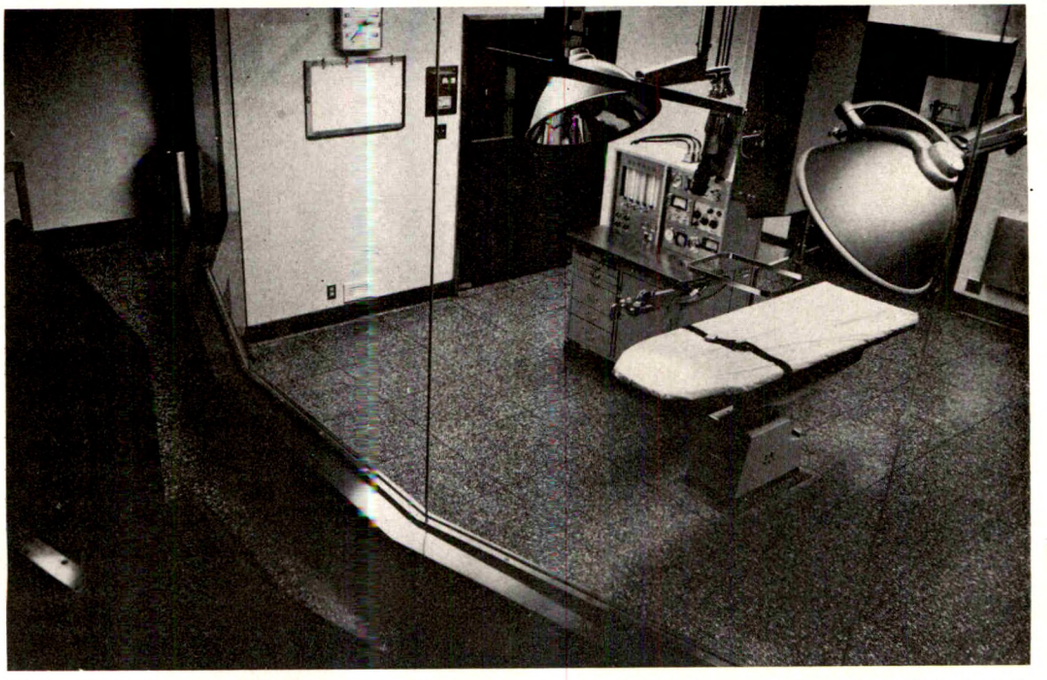


Fig. 3 (Christensen and Straatsma). Observation gallery. For optimum viewing the gallery floor is elevated; two rows of couches are arranged in tiers. Curved wall behind gallery and operating room is tempered plate glass.



Fig. 4 (Christensen and Straatsma). Observation gallery television. High resolution television cameras are mounted on the twin light and surgical microscope. The image of both cameras is viewed on monitors (upper right), recorded on television tape, and displayed simultaneously on a 21-inch monitor in the operating room and on a 14-inch monitor in the gallery (foreground).

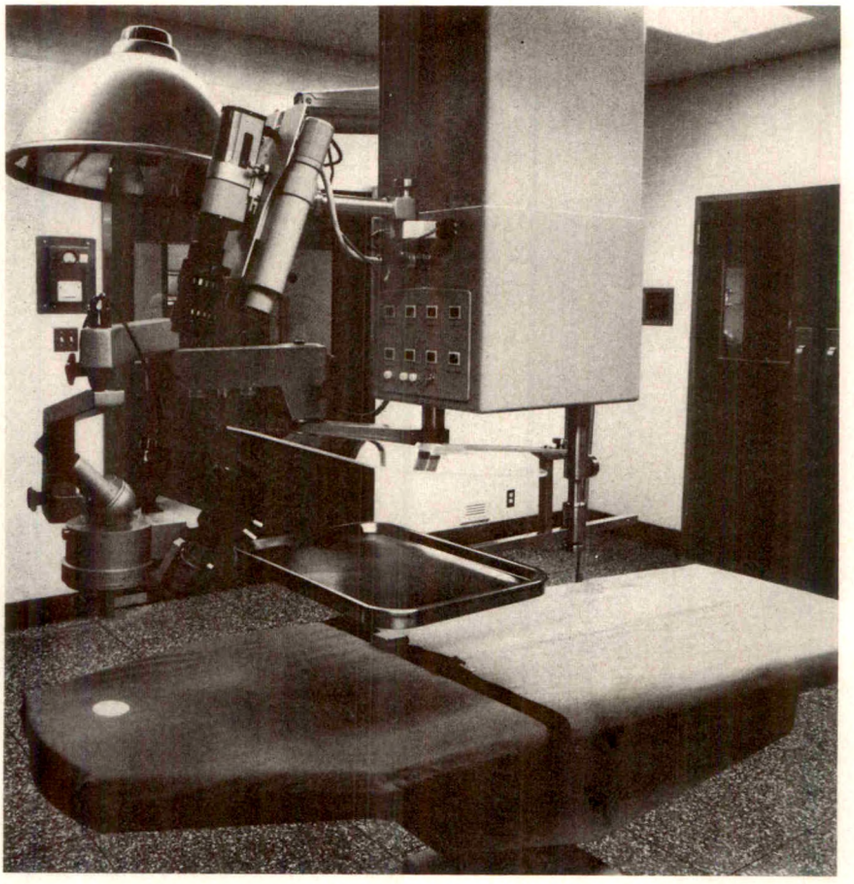


Fig. 5 (Christensen and Straatsma). Equipment column. Main column is adjustable and provides support for the surgical instrument tray with canopy, twin light and coaxial television cameras, and the surgical microscope. On the front of the column are outlets to which sterile surgical instruments may be attached and illuminated indicators to inform the surgeon of foot control settings.

nected with both the columns and the pedestal (Fig. 4).

The main column, which may be raised or lowered, supports the surgical instrument tray with its sterile transparent canopy, the high-intensity twin light and coaxially-mounted television camera, and the surgical microscope. The microscope is independently mounted so it can be focused or adjusted up and down and the "zoom" magnification varied by the surgeon's foot controls, which extend from the fixed surgical pedestal (Fig. 5).

On the front of the column facing the surgeon are outlets to which sterile surgical instruments for cautery, diathermy, vacuum, and the erysiphake lens extractor may be attached (Fig. 5). These items are contained in a recessed equipment cabinet and control console connected to the main column and to the pedestal by concealed conduit and cables (Figs. 4 and 6). The control-console selectivity connects the units and the operating microscope with the foot controls, regulates television transmission to the tape recorder, and monitors and adjusts audiocommunication with the gallery (Fig. 6).

On the side of the column are connections for television cameras attached to the twin light and to the operating microscope, a 16-mm movie camera, a 35-mm still camera, and microphones for use by the surgeon. On the

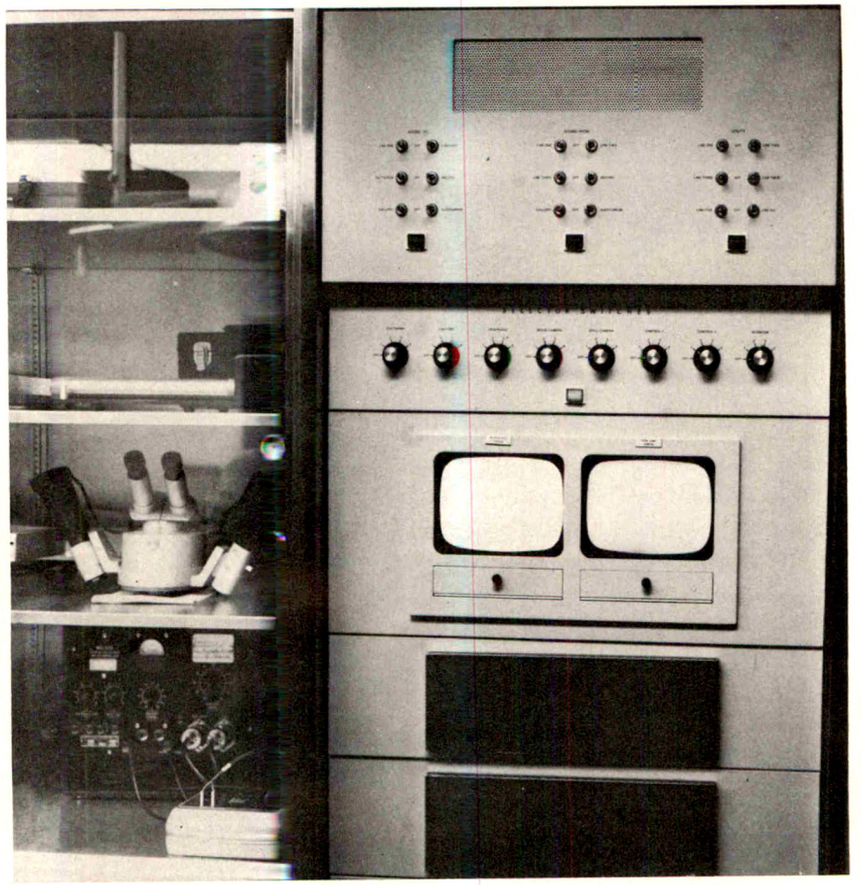


Fig. 6 (Christensen and Straatsma). Equipment cabinet and control console. Connected with the equipment column and the fixed surgical pedestal are a cabinet for surgical equipment (left) and a control console (right). The latter connects the equipment with the foot controls preferred by the surgeon, regulates the television system, and adjusts audiocommunication with the gallery.

back of the column are switches for the twin light, ceiling lights, and paired Castle surgical lights, controls to adjust the elevation of the main column, auxiliary column, operating table, and the head of the operating table (Fig. 7).

One control automatically adjusts all the elements needed to transfer a patient to or from the special wheeled stretcher to the pedestal. All controls operate by simple pressure, so they can be activated by the circulating nurse or depressed by the scrub nurse without contamination.

A safety device incorporated into the system prevents the theoretical possibility that a patient might be inadvertently compressed between the operating table and the column. Upon the exertion of one pound of pressure on the lowest projection of the column, the column moves up automatically as the table simultaneously moves down. Until the safety is reset, this control for position of the column and the table is preponderant over all controls.

The pedestal also incorporates electrical outlets, electrical ground circuits, a source of suction for surgery and anesthesia, and built-in sources of compressed air, oxygen, and nitrous oxide (Fig. 7). On the upper surface of the pedestal, two locking pins engage the contoured surgical table top, and four electromagnets hold it firmly in place

(Fig. 4). With the table attached, the pedestal may be adjusted by using controls on the main column, allowing the surgeon to sit or stand and the patient to be placed in Trendelenburg or reverse Trendelenburg position.

Movement of the pedestal and the columns is controlled by a hydraulic system located beneath each of the elevated observation galleries. An interlink between the two units permits the equipment in both special operating rooms to be operated by either hydraulic system.

The surgeon's chair is an integral part of a system in which foot controls are used and surgery is performed under high magnification (Fig. 8). The chair is designed to move easily when unoccupied and to be extremely stable when in use. The large base plate and unique pivot point enable the surgeon to rotate the chair to left and right through an arc greater than 90 degrees, while remaining concentric with the surgical field. The chair height is adjustable, and each arm support can be adjusted up, down, in and out, or removed entirely. When in use, the arm supports are covered completely with sterile drapes. When not in use, the surgeon's chair is stored beneath the observation gallery (Fig. 7).

Recessed in the wall opposite the corridor are the control console, surgical equipment cabinet, racks of sterile instruments, sutures and supplies, and cabinets containing surgical packs, as well as waste containers, low-intensity floor lights, and a wall-mounted stool and writing board for use by the circulating nurse (Fig. 7). On other walls of the room are x-ray view boxes, a clock with sweep-second hand, a stainless steel drop-leaf table on which surgical gowns and

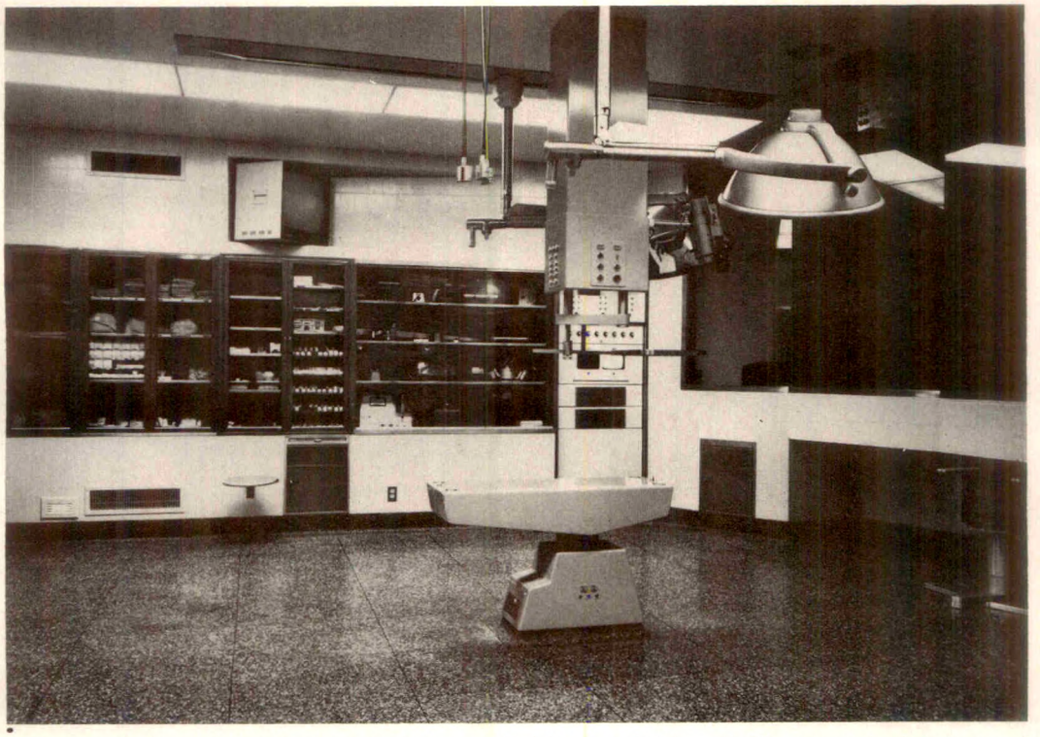


Fig. 7 (Christensen and Straatsma). Gallery wall (right) and side wall. The surgeon's chair is stored in a recessed space beneath the observation gallery. Side wall contains (from right to left) the control console, equipment console, racks of sterile instruments, sutures, and complete surgical packs. Also visible are recessed containers for waste, low intensity floor lights, and a wall mounted stool and writing board for the circulating nurse.

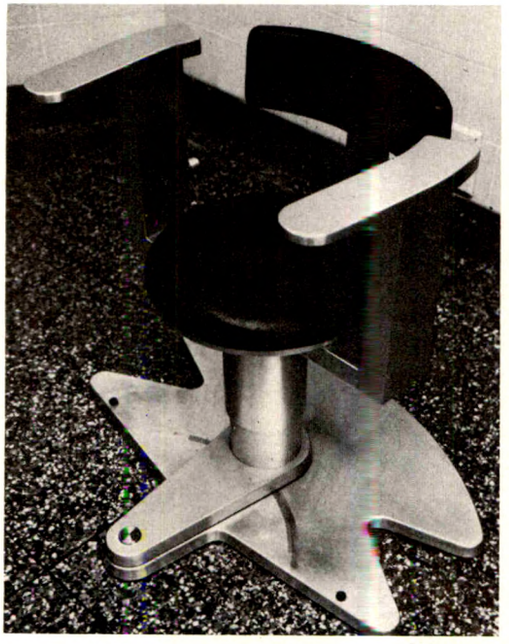


Fig. 8 (Christensen and Straatsma). Surgeon's chair. A large base plate and unique pivot point enable the surgeon to rotate this chair through an arc of more than 90 degrees while remaining concentric with the surgical field. Chair height may be varied with a built-in hydraulic control and each arm support may be adjusted up, down, in and out, or removed entirely.

gloves are placed at the beginning of each procedure, and doors connecting the operating room with the anesthesia induction room, surgical scrub area, and main corridor (Fig. 4).

The ceiling plan is of increasing importance in the design of an operating room. In this operating room, the ceiling incorporates the main column, the auxiliary column, ceiling outlets for oxygen, nitrous oxide and suction, and three sets of lights (Figs. 4 and 7). Supplementing the high-intensity Zeiss twin lamp on the main column are a pair of Castle surgical lights suspended from recessed ceiling tracks, two banks of fluorescent lights designed to provide optimum overall level of illumination in the room, and two recessed battery-operated emergency lights. The latter are designed to receive electrical energy from large, constantly charged storage batteries and to turn on automatically upon simultaneous failure of the regular power source and the stand-by hospital generator.

Anesthesia gas flows in from the ceiling or from the fixed pedestal attached to an anesthesia console developed for the Institute (Figs. 3 and 9).[5] This machine connects to built-in gas supplies and contains anesthesia gas-flow meters; stand-by tanks of oxygen, nitrous oxide, and medical compressed air; vaporizers for halothane and methoxyflorane; a carbon dioxide absorption system with bacteria filter; suction equipment; and a Bird automatic ventilator.

The unit contains an operation timer and equipment to monitor the patient's blood pressure, pulse rate, electrocardiogram, and blood oxygen saturations. Drawers of the console contain syringes, medications, and supplies; a voice-actuated tape recorder for educational and forensic purposes; and a writing surface for anesthesia records.

Augmenting the specially equipped ophthalmic operating rooms is a standard operating room, 400 square feet in size, for procedures which do not require special equipment. Photocoagulation therapy with the Zeiss zenon arc photocoagulator and the ruby laser (American Optical Co.) is carried out in this space. Space allocated for a fourth operating room is currently unfurnished.

Between the present and future operating rooms are anesthesia induction rooms and surgical scrub areas (Figs. 10 and 11). The anesthesia induction areas are equipped with wall-mounted anesthesia units. Through a large glass window, the surgical team can observe induction of general or local anesthesia, preparation of the surgical area, and placement of some or all surgical drapes, from the adjacent surgical sbrub area (Fig. 11). In the event of an emergency during induction of anesthesia, this observation permits immediate response. The surgical scrub area also contains a high-speed autoclave for resterilization of an instrument, if necessary, during a surgical procedure.

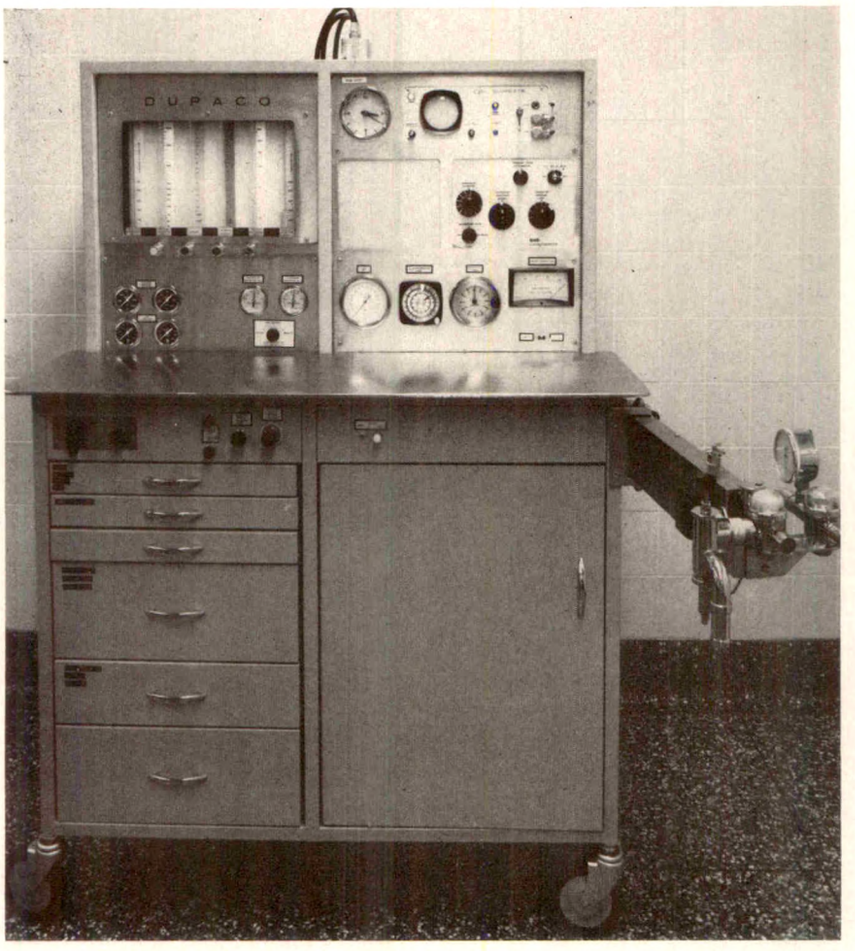



Fig. 9 (Christensen and Straatsma). Anesthesia console. The anesthesia unit connects with built-in gas supplies (top) and contains anesthesia gas flow meters (top left); patient monitor and timing equipment (top right); drawers and pullouts for syringes, medications, record keeping, and a voice-actuated tape recorder (bottom left); plus standby gas tanks, absorption system suction equipment, and ventilator (bottom right). The anesthesia bag and connecting tubes are attached to the arm that projects toward the patient (far right).

Equally accessible to all operating rooms is an instrument preparation room, divided into a "dirty" and a "clean" area (Fig. 1). Linen and waste used in a surgical procedure are transferred to the "dirty" area, placed in hampers, and removed through special doors that open directly into the outer support zone.

An ultrasonic cleaner-sterilizer that functions like a conveyor belt transmits surgical instruments to the "clean" area, where they are inspected and combined with other items to make up complete packs for specific surgical procedures.

*Surgical patient transportation*—The system for the transportation of patients consists of a commercially available Surgilift with break-apart conductive vinyl top, a specially designed stretcher with detachable top, and the fixed operating room pedestal.

The patient is moved from the hospital bed in the inpatient unit to the Surgilift[12] and transported to the surgical suite. In the corridor adjacent to the induction room, the

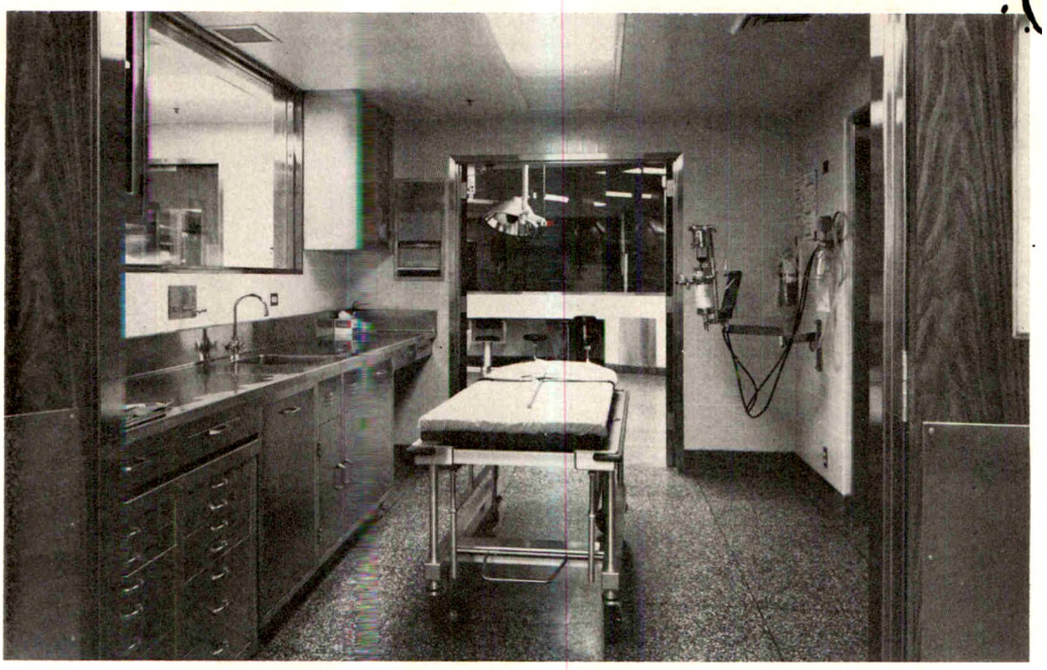


Fig. 10 (Christensen and Straatsma). Anesthesia induction room. Equipped with a wall-mounted anesthesia unit (right), the room is used for induction of local or general anesthesia, preparation of the surgical area, and placement of some or all surgical drapes.

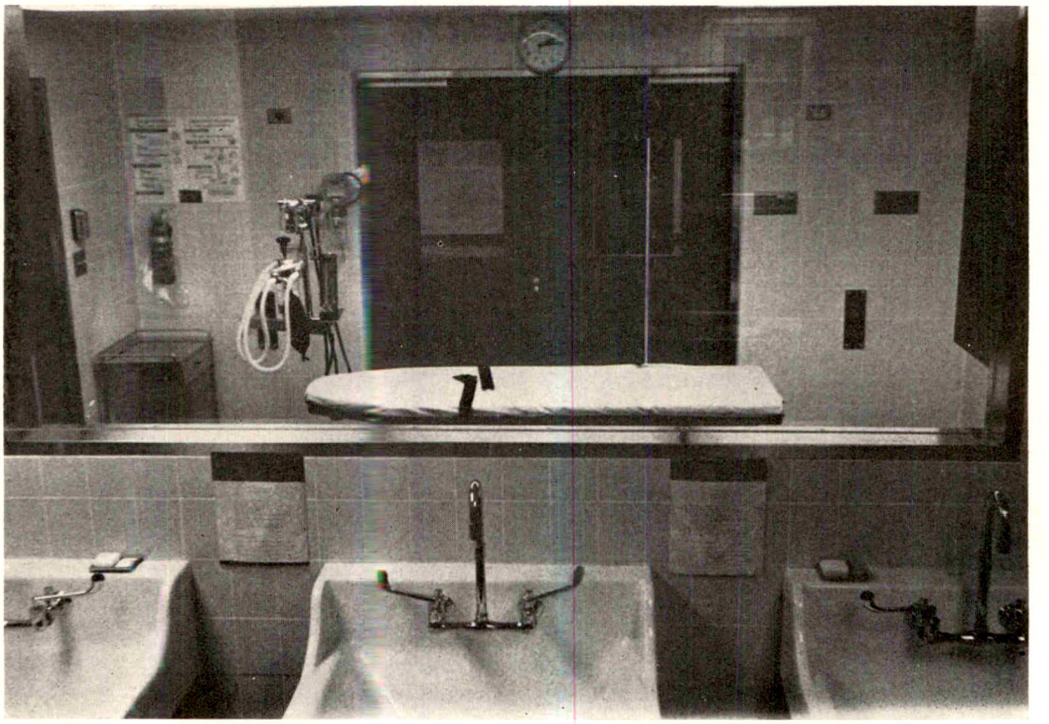


Fig. 11 (Christensen and Straatsma). Surgical scrub area. Through a large plate glass window, the surgical team can view the induction of anesthesia and the general preparation of the patient.

Surgilift is moved over the specially designed stretcher (Fig. 12) and the patient lowered onto the stretcher by means of a crank. When the straps on the circumference are released, the patient is precisely positioned on the stretcher.

The stretcher enters the induction room and, after the patient has received anesthesia induction, general preparation, and surgical draping, is moved into the operating room. The U-shaped stretcher (Figs. 10 and 12) is placed over the pedestal (Figs. 5 and 7), where the depression of a single control button transfers and firmly attaches the stretcher top to the pedestal (Fig. 4).

After the surgical procedure, the stretcher top is automatically replaced on the stretcher, side rails are attached, and the patient is transported to the recovery room. Except for the taper at the head, the stretcher is several inches wider than the usual operating table. Its two-inch pad of vinyl-covered conductive rubber enables the patient to remain comfortably on this unit in the recovery room.

When the patient is released from the recovery room, the Surgilift is reattached to the break-apart top (which has remained in place under the patient throughout surgery), and the patient is returned to the inpatient unit. Final transfer is made by lowering the patient onto his bed and releasing the circumference straps. When the center strip of the top is pulled out, the two sides are easily removed without disturbing the patient. This patient transport system avoids direct lifting of the patient by surgeon or assistants, eliminates physical strain by the patient in the immediate postoperative period, and is performed easily by one person.

Evaluation of a surgical system is a continuing process. The ophthalmic surgical system at the Jules Stein Eye Institute has increased patient safety, enhanced the precision of surgery, facilitated surgical training, and allowed for easy incorporation of equipment developed since inception of its design. Physicians with extensive experience in a variety of surgical methods have noted no significant defect in general design or in specially developed equipment. The response of nurses and paramedical personnel has been equally favorable.

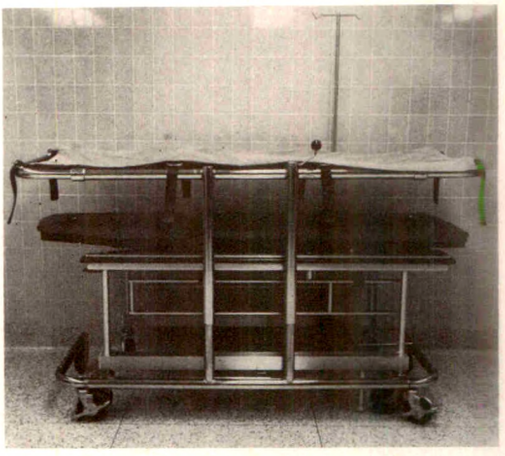


Fig. 12 (Christensen and Straatsma). The transfer from Surgilift to special surgical stretcher. After proper positioning, the Surgilift is lowered over the stretcher, the straps on circumference of break-apart top are released, and Surgilift frame is removed.

## Summary

The unique features of the ophthalmic surgery system at the Jules Stein Eye Institute include a support zone and two specially designed operating rooms. Hydraulic columns, pedestals, and equipment cabinets are interconnected by conduits. An adjustable hydraulic surgeon's chair rotates and remains concentric with the operative field. An anesthesia console provides gases and patient monitoring equipment. Closed circuit television and videotaping greatly aid observation of surgery in the operating rooms and galleries. The patient transport system includes a Surgilift, a stretcher with detachable top, and a fixed hydraulic operating room pedestal.

### Acknowledgments

Special operating room equipment was designed and constructed by Fred Storm Industrial Design, Inc., Los Angeles, California. The Surgilift is manufactured by Institutional Industries, Inc., 5500

Muddy Creek Road, Cincinnati, Ohio 45238. Mr. Michael Geoghegan made the photographs. Verona Pettyjohn provided editorial assistance.

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### Ophthalmic miniature

*EYE*—the Eyes are born in Armoury, as well as other parts of Man, for being so Principal a Part, that without them we are deprived of the enjoyment of all visible Objects, they are an Emblem of Vigilancy and Vivacity.

James Coats
*A New Dictionary of Heraldry*
London, 1747

# PERIPHERAL NASAL FIELD DEFECTS

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In 1909, Rønne[1] introduced the concept that peripheral nasal step defects are a specific visual field change in glaucoma. It was a logical and well-founded extension of the arcuate fiber defect theory postulated by Bjerrum[2] and widely accepted soon thereafter in ophthalmic circles. For the next few decades, the literature contained reports, reviews, and discussions amplifying the frequency and importance of this type of field defect. In recent years, however, attention has been directed to central field studies, while only passing mention of the nasal step defect has appeared in textbooks and in the literature. Little attempt has been made to define the step as originally conceived by Rønne,[3-5] and the defect was considered of little value in the diagnosis of glaucoma.[6-9]

The purpose of this study was to determine the frequency of characteristic peripheral nasal field defects with step-like features in glaucoma patients.

## MATERIAL AND METHODS

*Selection of patients*—Fifty-one consecutive patients with primary open-angle glaucoma and documented field loss, seen in consultation in the Glaucoma Center, were selected for this study.

*Methods*—All patients had a complete ophthalmic examination which included general medical, family, and ocular history; visual acuity; refraction; tonometry; tonography; ophthalmoscopic examination; and visual field studies on the Goldmann perimeter, using both static and kinetic techniques. The static perimetry was carried out according to the circular method described by Ourgaud and Aubert[10] at 5, 15, and 35 to 45 degrees eccentricity, using various size test objects. All positive findings were then confirmed by meridional static perimetry.

## RESULTS

In the 51 consecutive patients (101 eyes) with glaucoma, there were 81 eyes with characteristic glaucoma field loss (Table 1). Twenty-one eyes (26%) showed peripheral nasal field defects with step features. In 12 of the 21 eyes this peripheral defect was accompanied by a central defect as well, but in nine eyes (43% of those eyes with nasal steps) the peripheral nasal defect was an isolated finding. Thus, an isolated nasal step occurred in 11% of the 81 eyes with glaucomatous field defects.

## CASE REPORTS

Cases 1 and 2, described below, are illustrative of primary open-angle glaucoma in which the peripheral nasal step was the initial and only field loss.

*Case* 1—This 13-year-old black boy was first seen at McMillan Hospital in January, 1966. His visual acuity was 20/20 in both eyes with myopic correction. Fundus examination revealed myopic crescents and a cup/disk ratio of 0.7 in both eyes. Applanation intraocular pressure (mm Hg) was RE:22, and LE:20, and the tonographic tracing demonstrated outflow facilities of RE:0.07, and LE:0.05. Slit lamp examination was normal and gonioscopy revealed Grade IV open angles. Tangent screen examination demonstrated normal visual

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TABLE 1

PERIPHERAL NASAL FIELD DEFECTS IN EYES WITH GLAUCOMATOUS FIELD LOSS

| | Present Series | Aulhorn |
|---|---|---|
| Peripheral nasal field defects. | 21/81(26%) | 280/961(29.0%) |
| When accompanied with central defects | 12/81(15%) | 273/961(28.4%) |
| When isolated finding | 9/81(11%) | 7/961(0.7%) |

fields. The patient was classified as a glaucoma suspect on the basis of his pressures and outflow facilities and referred for further follow-up.

In December, 1967, Goldmann fields (Fig. 1) revealed an inferior nasal step of the right eye at 55 degrees using a I 4e test object and at 40 degrees when using a I 2e test object. In July, 1968, Goldmann field examination of the right eye was unchanged. Circular static perimetry, as well as meridional profiles above and below the horizontal meridian, confirmed the previously noted defects in the inferior nasal area of the right eye. The patient was classified as having primary open-angle glaucoma with field loss in the right eye and was begun on therapy.

*Case 2*—This 49-year-old black woman was found in 1961 to have high intraocular pressures and borderline facilities of outflow, but demonstrated no field loss at that time on tangent screen examination. Because of repeated intraocular pressures over 30 mm Hg, she was treated with antiglaucomatous therapy. In August, 1967, she was referred to the Glaucoma Center. Her corrected visual acuity was 20/20 in both eyes. Applanation pressures were RE:12, LE:13 mm Hg. Fundus examination revealed cup/disk ratios of 0.4 in the right eye and 0.7 in the left eye. Medication was discontinued. The patient returned three weeks later with applanation pressures of RE:18 and LE:28. Goldmann fields were normal in the right eye, but a nasal step was noted at 25 degrees eccentricity in the left eye, using a I 3e test object. Static quantitative perimetry was normal except for the superior nasal step in the left eye. The patient's visual fields were confirmed on repeated examinations on several occasions during the next few months (Fig. 2). The patient has been maintained on antiglaucomatous therapy with good control of pressure and no further deterioration in visual field function. The patient was classified as having primary open-angle glaucoma with asymmetrical pressures and field loss limited to the left eye.

Cases 3 and 4 illustrate primary open-angle glaucoma in which the visual field loss was a central defect accompanied by a peripheral nasal step.

*Case 3*—This 52-year-old white man was first seen on July 18, 1967, with a family history of glaucoma. Visual acuity with correction was RE: 20/20, and LE: 20/25. Applanation pressures were RE: 20, and LE: 18 mm Hg and outflow facilities were RE: 0.38, and LE: 0.33. Slit lamp examination was normal and gonioscopy revealed Grade IV open angles. Fundus examination showed myopic disks with a cup/disk ratio of RE: 0.1, and LE: 0.4. Visual field examination on the Goldmann perimeter was normal.

The patient returned one year later still asymptomatic. His applanation pressures were RE: 20, and LE: 21 mm Hg with outflow facilities of RE: 0.22, and LE: 0.20. Visual field examination was once again normal in the right eye. In the left eye, however, a nasal step at 40 degrees eccentricity extending to 50 degrees eccentricity was noted using the I 4e and the III 4e test objects. In addition, a superior Bjerrum scotoma was noted in the left eye using the I 2e test object (Fig. 3). Repeated visual field studies, using both kinetic and static techniques, confirmed the inferior nasal step as well as the superior Bjerrum scotoma in the left eye. The visual field has remained normal in the right eye. This patient has been followed on antiglaucomatous therapy.

*Case 4*—This 51-year-old white man was said to have glaucoma in 1951 and was treated intensively for three years. A maternal aunt had glaucoma. In July, 1954, visual acuity was RE: 20/20+, and LE: 20/20+. Tangent screen field examination showed minimal enlargement of the blind spots in both eyes to a 1 mm test object at one meter distance. Slit lamp examination was normal, as was

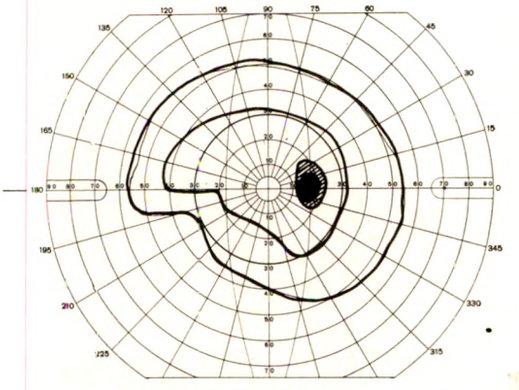


Fig. 1 (LeBlanc and Becker). Case 1. Visual field, right eye, showing nasal step.

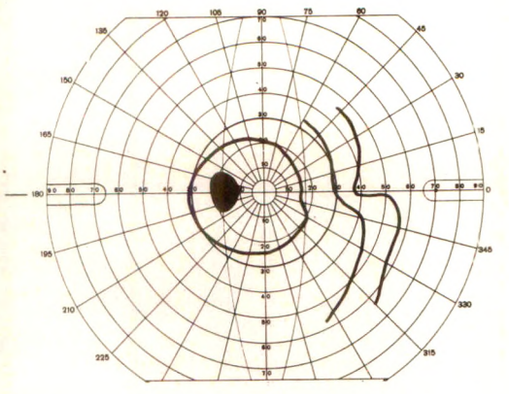


Fig. 2 (LeBlanc and Becker). Case 2. Superior nasal step in visual field of left eye.

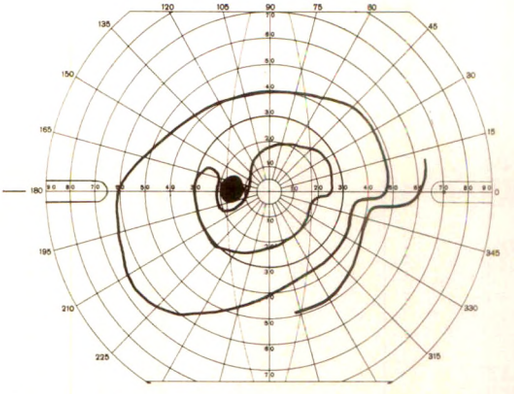


Fig. 3 (LeBlanc and Becker). Case 3. Superior arcuate scotoma accompanied by inferior nasal step.

the fundus examination. Gonioscopy revealed open angles. Applanation pressures were 38 mm Hg in both eyes with outflow facilities of RE: 0.04, and LE: 0.10. On maximum therapy his intraocular pressures could not be controlled. In October, 1963, his Goldmann field (Fig. 4) showed a sharp superior nasal step in the right eye with the I 2°, I 3°, and II 4° test objects. The patient also progressively developed marked glaucomatous cupping. Thermal sclerostomies were performed in the right eye in October, 1963, and in the left eye in January, 1964. In March of 1969, the visual acuity was RE: 20/300, LE: 20/200. Visual field examination of the right eye showed constricted isopters and a superior nasal step deformity present at 55 degrees eccentricity with a V 4° test object and at 50 degrees eccentricity with a II 4° test object. At 25 degrees eccentricity, the nasal step was present with a I 4° test object. To date, the left eye has demonstrated no nasal step. Applanation pressures were RE: 25, and LE: 10 mm Hg with outflow facilities of RE: 0.10, and LE: 0.31.

Cases 5 and 6 illustrate open-angle glaucoma with central visual field defects followed by late development of peripheral nasal steps.

*Case* 5—This 63-year-old white man was diagnosed as having primary open-angle glaucoma in 1955 on the basis of intraocular pressures. The patient was placed on antiglaucomatous therapy with fair control until May of 1966, at which time a relative Bjerrum scotoma in the left eye was found with a 1 mm test object on the tangent screen. In July, 1967, a Goldmann field showed the right eye to be normal, but the left eye showed a superior Bjerrum scotoma encroaching upon fixation with a I 2° test object. No nasal step deformity was noted at that time. His visual acuity in both eyes was 20/20 without correction. Slit lamp examination was normal. Gonioscopy revealed Grade IV open angles in both eyes. Fundus examination showed 0.3 cup/disk ratio in the right eye; the left eye showed a 0.5 cup/disk ratio with temporal pallor and a nasal shift of the vessels. The patient's investigation included ophthalmodynamometric studies and a neurologic work-up because of the asymmetrical field loss. All studies were normal. The patient's therapy was intensified. In May of 1968, visual field examination revealed further loss to the I 2° test object as well as the first appearance of a superior nasal step at 45 degrees eccentricity with the I 4° test object. Continued medical therapy since that time has prevented progression of the central field loss, but the superior nasal step has progressed (Fig. 5).

*Case* 6—This 48-year-old white man was diagnosed as having glaucoma in 1958 and placed on antiglaucomatous therapy. When referred in 1961, visual acuity was 20/20 in both eyes. Applanation pressures were RE: 31, and LE: 24 mm Hg, with facilities of outflow of RE: 0.06, and LE: 0.07. Slit lamp examination showed Krukenberg spindles and increased transillumination of the mid-periphery of the iris. Gonioscopy revealed Grade III open angles

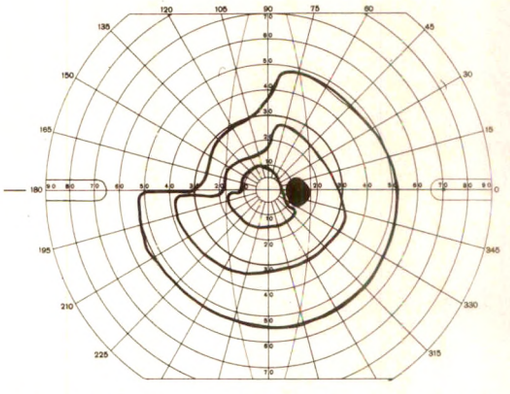


Fig. 4 (LeBlanc and Becker). Case 4. Chart shows both peripheral and central visual field loss and step feature.

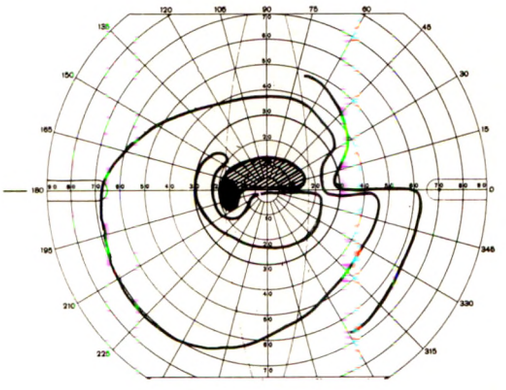


Fig. 5 (LeBlanc and Becker). Case 5. Well-developed arcuate scotoma and superior nasal field defect.

with heavy pigmentation of the trabeculum extending all the way to Schwalbe's line. Tangent screen examination demonstrated superior Bjerrum scotomas in both eyes. Fundus examination showed marked cupping with loss of the temporal rim of the disk in both eyes. A diagnosis of pigmentary glaucoma with marked field loss was made. The patient's therapy was increased and he was followed until 1964 at which time Goldmann fields demonstrated the marked superior Bjerrum scotomas in both eyes. In addition, in the left eye a superior nasal step at 40 degrees eccentricity with the I 4e test object and at 15 degrees eccentricity to the I 4e test object was noted (Fig. 6). The patient's antiglaucomatous therapy has been maintained and subsequent follow-up visits have shown good intraocular pressure control with no further changes in visual fields.

## Discussion

How does one explain the characteristic topography of the nasal step defect? The basic anatomy of retinal nerve fibers is the apparent key, a fact appreciated by Bjerrum and Rønne.[1,2] When an isolated peripheral bundle (fibers to the temporal retina) is selectively affected by disease, an isolated peripheral nasal step ensues. Similarly, involvement of a paramacular bundle leads to a central arcuate defect ending in a sharp step feature at the horizontal meridian. Combinations of these two mechanisms result in central and peripheral steps, alone or in combination. The variety of the presentations of the nasal step is illustrated (Figs. 1-6).

Our findings agree with the report of Rønne[1] and leave no question as to the importance of the nasal step defect. Since many ophthalmologists confine their visual field testing in glaucoma patients to an evaluation of the central field, it is important to appreciate the relative frequency of peripheral nasal steps.

A recent and widely quoted study by Aulhorn and Harms[8] reports the field changes in 1561 glaucomatous eyes with field loss. The authors report general concentric contraction as the most common finding, a change said to be nonspecific for glaucoma and of little diagnostic value. Of 961 eyes with specific glaucomatous defects (Table 1), 280 (29%) present peripheral nasal contractions. Peripheral contractions, specifically from the nasal side, are reported as an isolated finding in only seven of these cases (0.7%), while in 273 cases (28.4%) nasal defects are accompanied by paracentral defects. It appears then that the frequency of peripheral nasal field defects in our small series compares well with that in the extensive report of Aulhorn (i.e., 26 vs 29%). However, isolated nasal defects are very rare in the large series but constitute half of the nasal defects we find. This discrepancy may be explained on the basis of a higher yield of paracentral scotomas by the Aulhorn and Harms group. They use the Tübingen perimeter which allows a more scrupulous search of the central areas for minute scotomata. However, the Tübing-

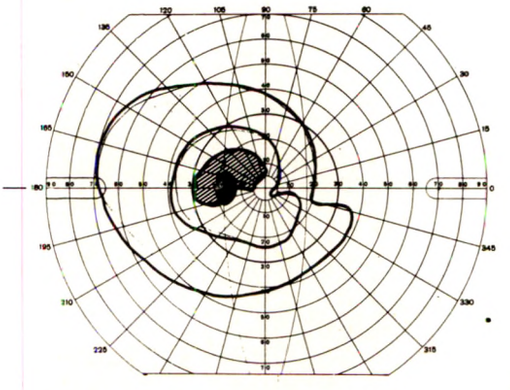


Fig. 6 (LeBlanc and Becker). Case 6. Superior arcuate defect with well-demarcated nasal step defect.

en perimeter is of limited availability compared to the more frequently used Goldmann and arc perimeters. In spite of intensive efforts with the Goldmann perimeter, using both static and kinetic techniques, we fail to demonstrate central defects in over 40% of patients with proved nasal steps. It is in this context that the importance of isolated peripheral nasal steps must be emphasized as a useful and early diagnostic sign in many cases of glaucoma.


## Summary

Fifty-one consecutive patients with primary open-angle glaucoma had 81 eyes with glaucomatous field loss. Peripheral nasal step field defects were found in 21 eyes (26%) and in nine of these the nasal step was the only demonstrable glaucoma field defect.


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### Ophthalmic miniature

An eye is for all the world exactly like a cannon, in this respect: That it is not so much the eye of the cannon, in themselves, as it is the carriage of the eye—and the carriage of the cannon, by which both the one and the other are enabled to do so much execution.

Lawrence Sterne
*Tristram Shandy*, 1760

# LIGHT AND ELECTRON MICROSCOPY IN ABSOLUTE GLAUCOMA WITH PIGMENT DISPERSION PHENOMENA AND CONTUSION ANGLE DEFORMITY

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*New York, New York*
AND
ERNST LANDOLT, M.D.
*Zurich, Switzerland*

Pigment deposit on the trabecular region has long been noted in relation to glaucoma, and its possible derivation from the pigment epithelium of the iris has also been considered.[1,2] While there were those who apparently did not give much attention to the relation between Krukenberg's spindle and glaucoma,[3] Sugar and Barbour[4] delineated a disease entity called pigmentary glaucoma. Since then, many reports of similar cases have accumulated, as recently reviewed by Sugar.[5] Pigmentary glaucoma tends to occur bilaterally in eyes of young myopic males with symptoms of depigmentation of the iris, Krukenberg's spindle, pigment deposition on an open-angled trabecular area, and glaucoma. In regard to the pathogenesis, no clear agreement has yet been attained. Opinions concerning a causal relation between the pigment and the glaucoma are various:

(1) Atrophy of pigment epithelium of the iris, and probably the ciliary body as well, is the main source of pigment deposition and subsequent glaucoma.[5-7] (2) Some underlying factors other than pigment deposition may play a main role in causing glaucoma.[8-14] (3) This type of glaucoma may possibly be a variant of primary open angle glaucoma,[15,16] and pigment dispersion may not cause the pressure elevation.[16] (4) The relation is not yet clear.[17] Apart from pressure elevation, however, a main factor of this disease is a pigment dispersion syndrome or phenomena, which consists of atrophy of the iris pigment epithelium, Krukenberg's spindle, a dense trabecular pigment ring, and deposits of pigment on the iris and lens capsular surfaces.

On the other hand, a relation between monocular glaucoma and chamber angle deformities due to ocular contusion was emphasized recently by Wolff and Zimmerman,[18] and such a deformity with recessed chamber angle caused by blunt trauma was confirmed by many followers.[19-27]

This paper reports the electron microscopy of the trabecular meshwork, iris, and cornea of a patient whose left eye was enucleated because of pain and absolute glaucoma, and in which eye we saw definite signs of pigment dispersion phenomena superimposed on those of angle deformity due probably to old ocular contusion.

## CASE REPORT

A 52-year-old patient had a history of progressive visual loss in his left eye for about five years. This eye was totally blind, with a tension of 50 mm Hg by applanation. The cornea was clear, with much pigment deposition on the posterior surface in the form of Krukenberg's spindle. The chamber angle was open with heavy pigmentation of the trabecular meshwork. The iris was slighly atrophic and a year later showed neoformation of blood vessels; at this stage, the patient complained of great pain. The blind eye was, therefore, removed. The right eye was found to have normal vision with 0.75 D hyperopia, and a normal visual field, but gonioscopically there were the same changes as in the left eye. There was also a typical Krukenberg's spindle on the corneal endothelium, and a slight iris atrophy was noticed by transillumination. Ocular pressure of this eye without therapy was 26 mm Hg

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at maximum, and could be kept around 15 mm Hg (applanation) with medication of one drop of adrenaline daily. The fundus showed no pathologic changes. An absolute pigmentary glaucoma of the left eye and beginning pigmentary glaucoma of the right eye was suspected clinically. As an early but important anamnesis, however, this patient had been hospitalized because of commotio cerebri due to a motorcycle accident about 26 years previously.

## Materials and methods

The enucleated left eye was immediately cut in half in a vertical meridian, and the temporal half with optic nerve was fixed in formalin and submitted to usual histopathologic study. Portions of the nasal half were fixed, either with 1% osmium tetroxide buffered with sucrose-containing Veronal acetate[28] or 2.5% glutaraldehyde in 0.05 M phosphate buffer (pH 7.4) followed by 1% osmium tetroxide,[29] dehydrated with graded alcohol and embedded in durcupan ACM (Araldite). Tissues were cut in meridional sections; 1-2 μ sections were stained with Giemsa for light microscopy and thin sections were doubly stained with uranyl acetate and lead citrate for electron microscopy as previous.[30] The LKB-Ultrotome and Porter-Blum microtome were used for cutting and the Zeiss EM-9 and EM-9S for electron microscopy. Normal human irises obtained by surgical enucleations due to malignant tumors were used as controls for the electron microscopy.

## Observations

### Light microscopy

Marked pannus was noted in the periphery of the cornea. A few scattered pigment granules were seen within the corneal endothelium. Although small pigment-clumps were occasionally attached to the posterior surface of the corneal endothelium, a large mass of such pigment granules was found in only one tissue block which was prepared originally for electron microscopy. This large accumulation was confined to a limited area of the central cornea, and believed to be clinical Krukenberg's spindle. The anterior chamber angle was open. Abundant pigment granules were deposited on the trabecular meshwork, which was sclerotic and degenerative. A hyaline membrane and an endothelium covered the entire inner surface of the trabecular region (Fig. 1-B), and the endothelium appeared to be continuous with that of the cornea. A deep recession of the chamber angle was seen in many areas (Fig. 1-A). The iris, ciliary body, and choroid were atrophic. In the iris both the stroma and iris epithelium* were far thinner than normal, and in the stroma there were many clump cells. Small pigment clumps were occasionally seen on the iris and lens capsule surfaces. The retina was atrophic. Atrophy of the ganglion cell and nerve fiber layer was significant. Glaucomatous cupping of the optic disk and thickening of the pial septum of the optic nerve were marked.

### Electron microscopy

The trabecular meshwork, iris, and part of the corneal endothelium were studied with the electron microscope.

*Trabecular meshwork*—The entire inner surface of the trabecular region was covered by an endothelium and a hyaline membrane (Figs. 1-C and 2-A). The endothelium was similar, structurally, to that of the normal corneal endothelium (Iwamoto and Smelser[31]), but there were some differences as follows: the thickness of the layer was irregular and, in general, thinner than that of normal central cornea (Figs. 1-C, 2-A and B). The tight junctions at the basal region of the intercellular spaces were often shorter or incomplete (Fig. 1-C). In the cytoplasm, there were more developed rough-surfaced endoplasmic reticulum, prominent filaments and some engulfed pigment granules (Fig. 2-B). A cilium-like structure was also occasionally found. The hyaline membrane varied in thickness and sometimes was very

* The iris epithelium consists of two pigmented layers: the anterior epithelial or myoepithelial (dilator muscle) layer, which is continuous with retinal pigment epithelium, and the posterior epithelial layer, or so-called iris pigment epithelium, which is a continuation of retinal neuroepithelium.

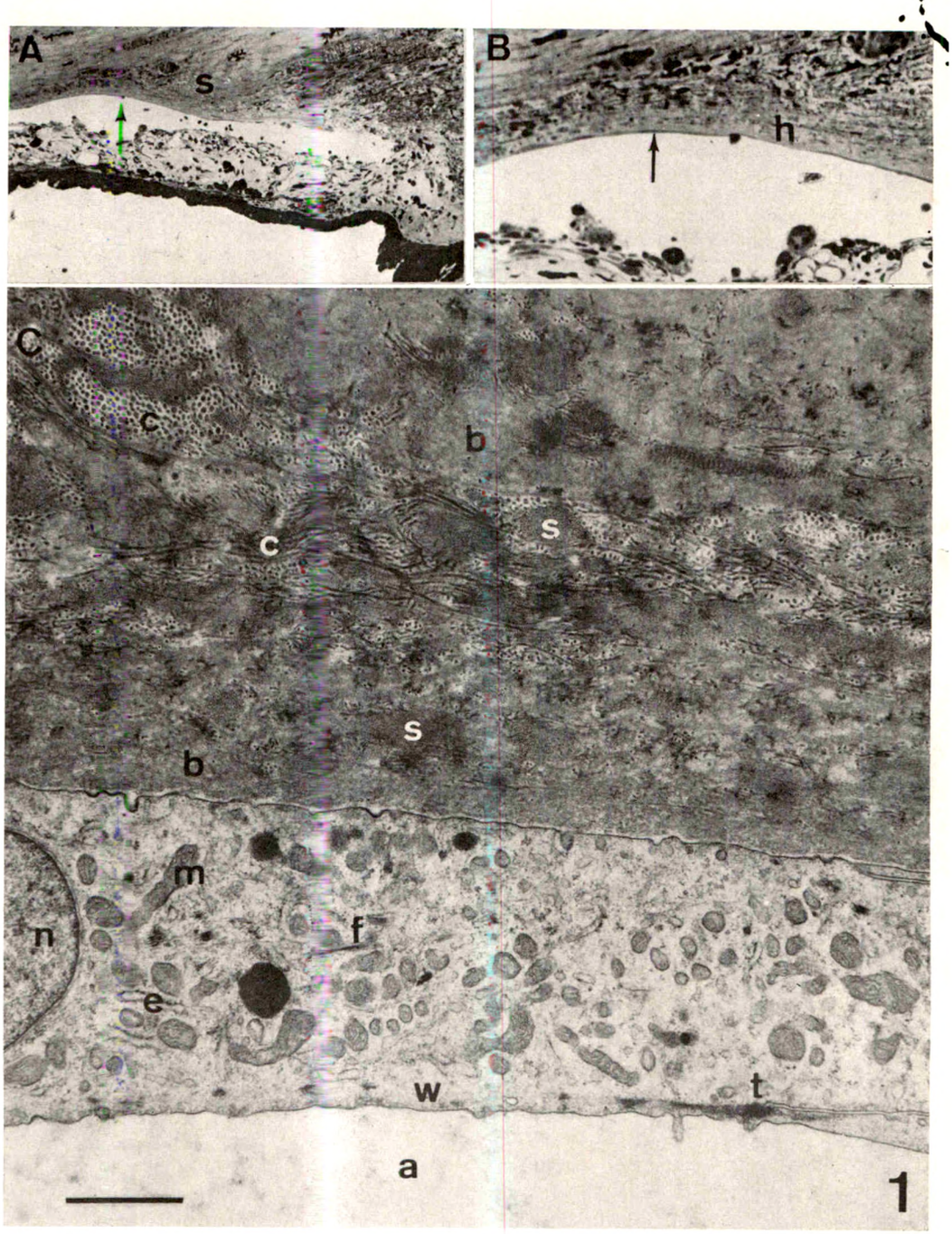



Fig. 1 (Iwamoto, Witmer, and Landolt). (A) Light micrograph of 2 μ section stained with Giemsa, showing the anterior chamber angle. Arrow indicates the trabecular region; (s) scleral spur. Note a deep recession of the angle (Giemsa, ×770). (B) Higher magnification of the trabecular region in A, showing the hyaline membrane (h) and endothelium (arrow) which cover the inner surface of the trabecular meshwork (Giemsa ×250). (C) Electron micrograph of the endothelium and hyaline membrane area. In the endothelium, nucleus (n), mitochondria (m), endoplasmic reticulum (er), terminal web (w), some filaments (f), and a tight junction (t), which is short, are seen. The hyaline membrane here is thick, and consists mainly of thin fibrils (s), thicker collagen fibrils (c), and basement membrane-like material, (b), (a) anterior chamber (×17,700). The line (bottom, left corner) in each electron micrograph (Figs. 1-7) represents 1 μ, unless otherwise indicated.

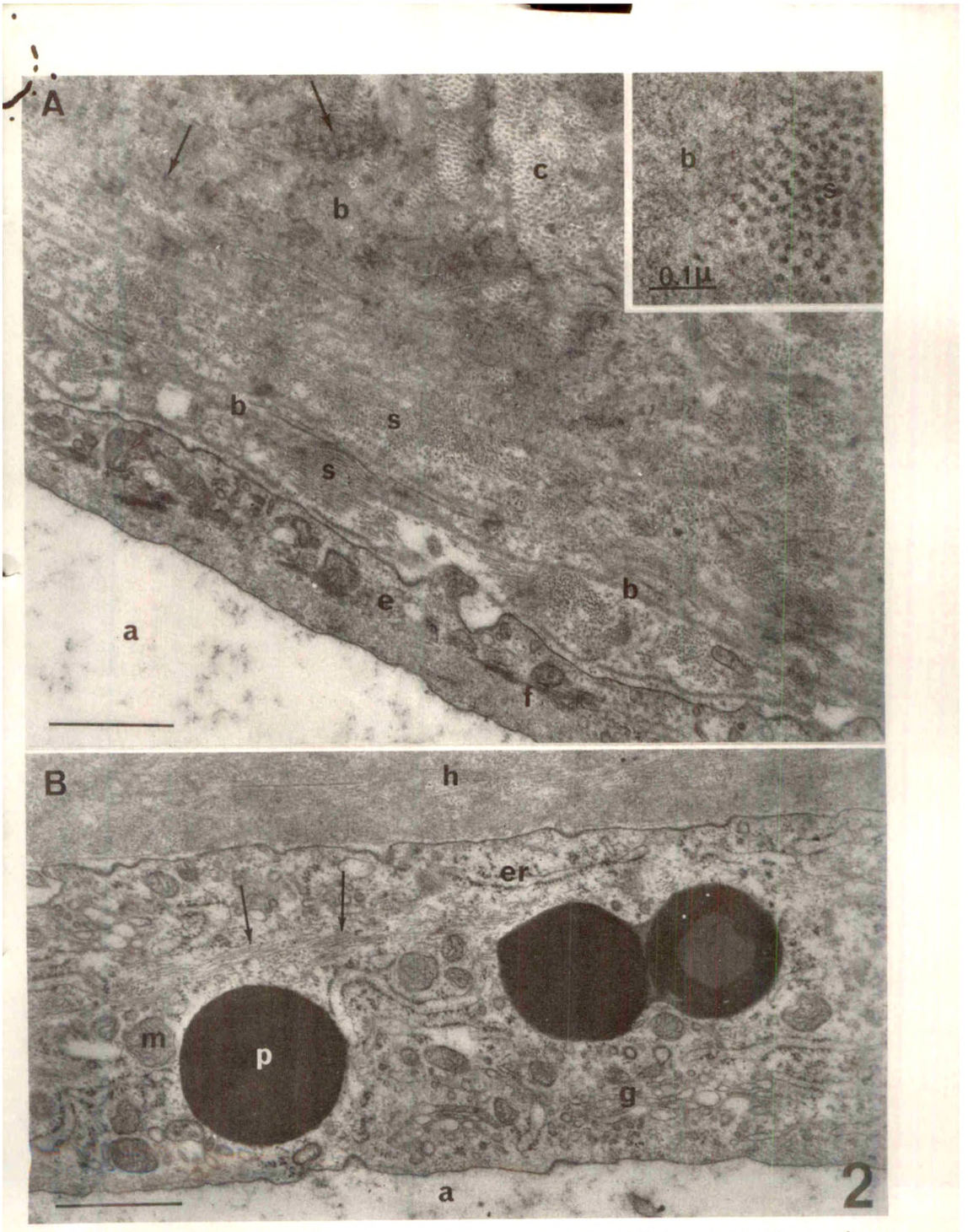



Fig. 2 (Iwamoto, Witmer, and Landolt). (A) Another region of endothelium and hyaline membrane covering the trabecular inner surface. The endothelium (e) is thin, and has filaments (f). The hyaline membrane consists of thin fibrils (s), thicker fibrils (c), basement membrane-like material (b) and some 100 nm banded material (arrows). This region is similar to abnormal Descemet's membrane of Fuchs' dystrophy (×20,000). Inset shows cross sections of the thin fibrils (s) and basement membrane-like material (b) at higher magnification (×108,000). (B) Another endothelial cell showing engulfed pigment granules (p), well developed rough-surfaced endoplasmic reticulum (er), and filaments (arrows), (m) mitochondria, (g) Golgi complex, (a) anterior chamber, (h) hyaline membrane (×20,000).

thick, as shown in Figure 1-C. It consisted of a mixture of basement membrane-like material, irregular groups of thin fibrils (10-15 nm in diameter), those of thicker collagen fibrils, and some 100 nm banded material. The basement membrane-like material was seen either as thin layers or widely spread areas. The hyaline membrane area made a transition into the innermost trabecular beams, which often lacked accompanying endothelial cells (Fig. 3-B).

In the uveal and corneoscleral meshwork, the individual beams or sheets contained abundant 100 nm banded material, mostly in the region called homogeneous matrix[32] or clear zone[33] (Fig. 3-A). The intertrabecular spaces were still open in some portions (Fig. 3-A), but in other areas the beams were closely apposed to each other, leaving a narrow space, or none, in between. In areas with no interspaces, either a single layer of endothelial cells separated the adjacent beams or the two beams fused without intervening cells (Fig. 3-B). The endothelial meshwork,[34] or juxtacanalicular connective tissue,[35] filled with cells and fibrillar elements often formed a thick layer (Fig. 4-A). No large vacuoles were observed in the endothelial cells lining the inner wall of Schlemm's canal. In some portions, the entire field of the trabecular meshwork was compactly filled with beams and other tissue elements without any space between the anterior chamber and Schlemm's canal (Fig. 3-B).

Cells containing pigment granules were frequently seen throughout the trabecular meshwork. They could roughly be divided into two types: In one type, pigment granules were distributed throughout the cytoplasm (Fig. 4-B); some of such cells resembled the clump cells seen in the iris, described below (Fig. 4-A). The other type of cells contained pigment granules aggregated in groups (Fig. 4-C), with each group clearly delimited from the surrounding cytoplasm. This type may be called macrophage.[36-38] The majority of these pigment granules observed in the trabecular area were of large, pigment-epithelial type, and the smaller granules, similar to those contained in the iris chromatophore or melanocyte, were only occasionally seen within the aggregates of the above macrophages (Fig. 4-C). Many of such pigment-containing cells covered the trabecular beams, at least in parts (Fig. 4-B).

*Iris*—Electron microscopy confirmed light microscopy in showing that both the stroma and the iris epithelium (dilator muscle layer plus iris pigment epithelium) were thinner than those of the normal control human irises. In the anterior border layer, so-called chromatophores, or uveal melanocytes, formed a relatively thick layer. The most significant finding in the stroma, however, was the presence of a large number of clump cells (Figs. 5-A and B). The majority of these belonged to the clump cells in the first phase, according to our tentative classification reported earlier (Iwamoto[38,39]). Most pigment granules contained in these cells were of the same size and structure as those of the iris epithelial cells, and were distributed throughout the cytoplasm. The other types of clump cells (Iwamoto[38,39]), were only occasionally observed (Fig. 5-C). In addition to these, clearly identifiable macrophages, as seen in the trabecular tissue (Fig. 4-C), were also found in the stroma.

Many of the myoepithelial or dilator muscle cells decreased or lost their anterior cytoplasmic (or muscular) processes, which are normally nonpigmented or only sparsely pigmented, and frequently, the whole cytoplasmic portions were filled with pigment granules. Various changes were seen in the iris pigment epithelial layer as well, while there were areas which appeared almost normal. These changes included: (1) apparent disintegration of the pigment granules (Fig. 6-A), seen also at the dilator muscle layer; (2) sparse distribution of the pigment granules in the cytoplasm (Fig. 6-B), and (3) destruction of the epithelial cell itself (Figs. 6-C and F), resulting in a release of the pig-

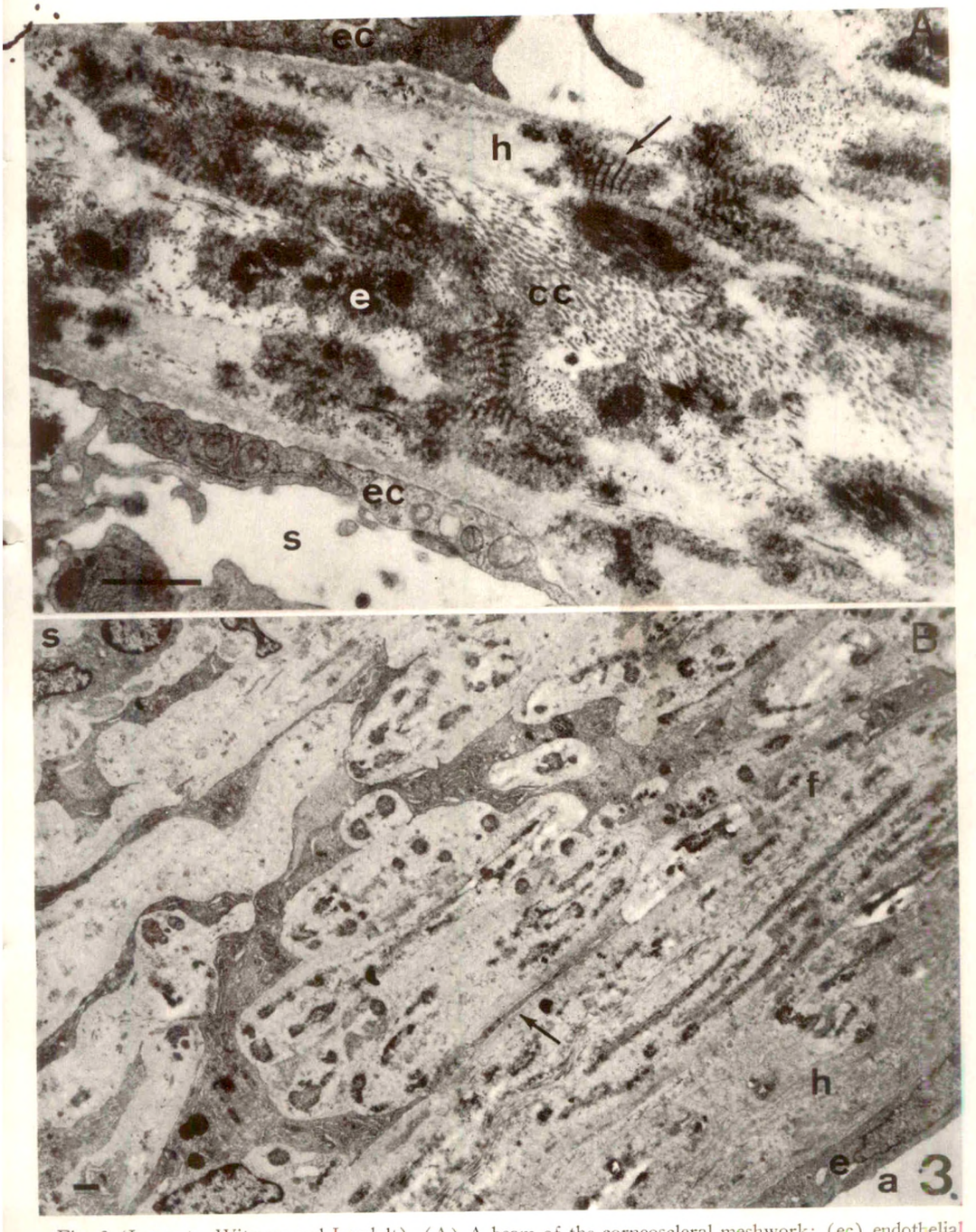



Fig. 3 (Iwamoto, Witmer, and Landolt). (A) A beam of the corneoscleral meshwork: (ec) endothelial cells covering the beam, (h) homogeneous matrix, (cc) central collagen core, (e) elastic component, (s) intertrabecular space. Note the abundant 100 nm banded material in the homogeneous matrix; the material appears to be located also in collagen core. (×14,700). (B) An area of the trabecular meshwork, where there is no intertrabecular space between the anterior chamber (a) and Schlemm's canal (s). A single thin layer of endothelial cells separates the adjacent beams at (arrow), and two beams are fused at (f). A hyaline membrane (h) which is covered by an endothelium (e) appears to make a transistion to the innermost trabecular beam. In this region only a few pigment granules are seen at lower left (×3750).

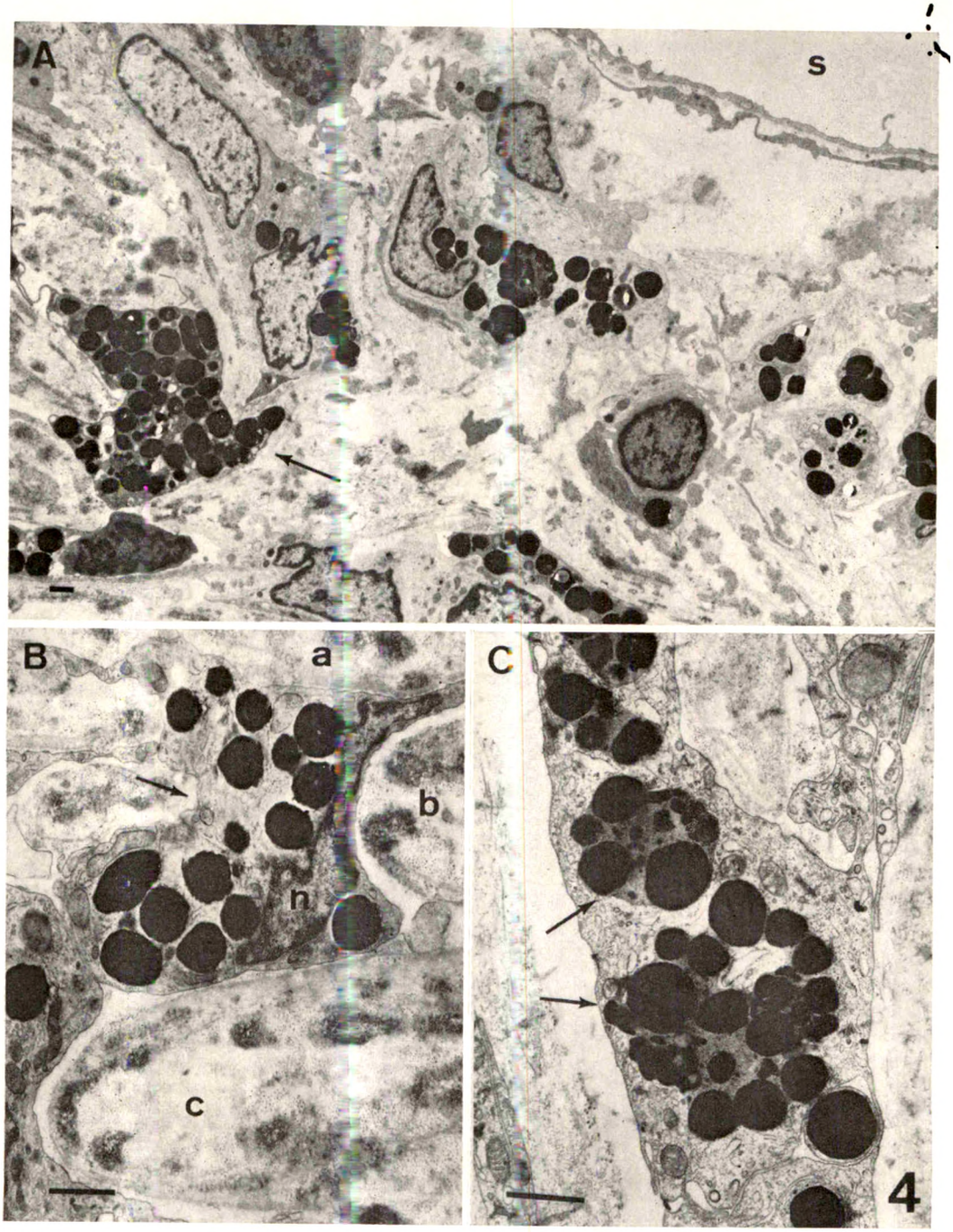



Fig. 4 (Iwamoto, Witmer, and Landolt). (A) A thickened area of the endothelial meshwork or juxtacanalicular connective tissue. Many pigment-containing cells are scattered in this region; one (arrow) assumes a structure similar to the clump cell seen in the iris. Majority of the pigment granules are of large, pigment-epithelial type, (s) Schlemm's canal (×3750). (B) A pigment-containing cell (arrow) in the corneoscleral meshwork. Pigment granules of large epithelial type are distributed throughout the cytoplasm. This cell covers parts of three different trabecular beams (a,b,c), (n) nucleus. (×9300). (C) A macrophage in the trabecular meshwork, containing several groups of pigment granules. Each group is clearly delimited from the surrounding cytoplasm, and composed of pigment granules embedded within a less dense granular matrix (arrow); most pigment granules are of large epithelial type, but some are smaller (×11,700).

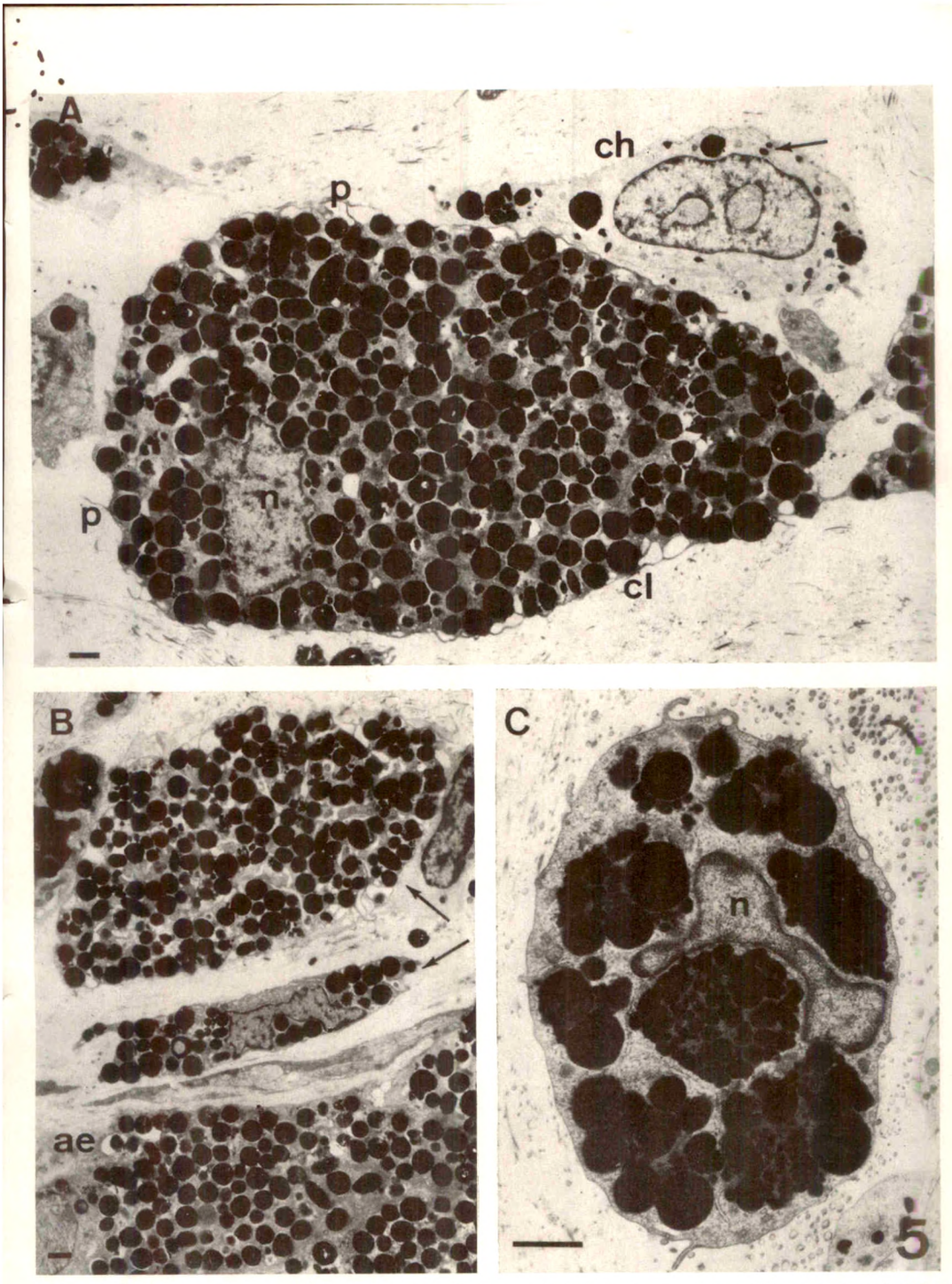



Fig. 5 (Iwamoto, Witmer, and Landolt). (A) A clump cell (cl) in the iris stroma. The cytoplasm is filled with pigment granules mainly of large epithelial type. Thin cytoplasmic processes (p) are on the cell surface; (n) nucleus. This type of clump cell had been classified as the first phase. On the upper right a chromatophore (ch) which has smaller pigment granules (arrow) is seen. This contains some larger granules which may have been phagocytosed. Similar chromatophores with a few large granules have sometimes been seen in this iris (×4600). (B) Two clump cells (arrows) of the same type as in A can be seen in the iris stroma near the anterior epithelial layer (ae) suggesting their derivation from the pigmented epithelial cells (×3230). (C) A pigment-containing cell in the iris stroma. It is filled with aggregates of pigment granules of various sizes, and may belong to the clump cell in the second or third phase. This cell is, however, difficult to distinguish from macrophage; (n) nucleus (×10,500).

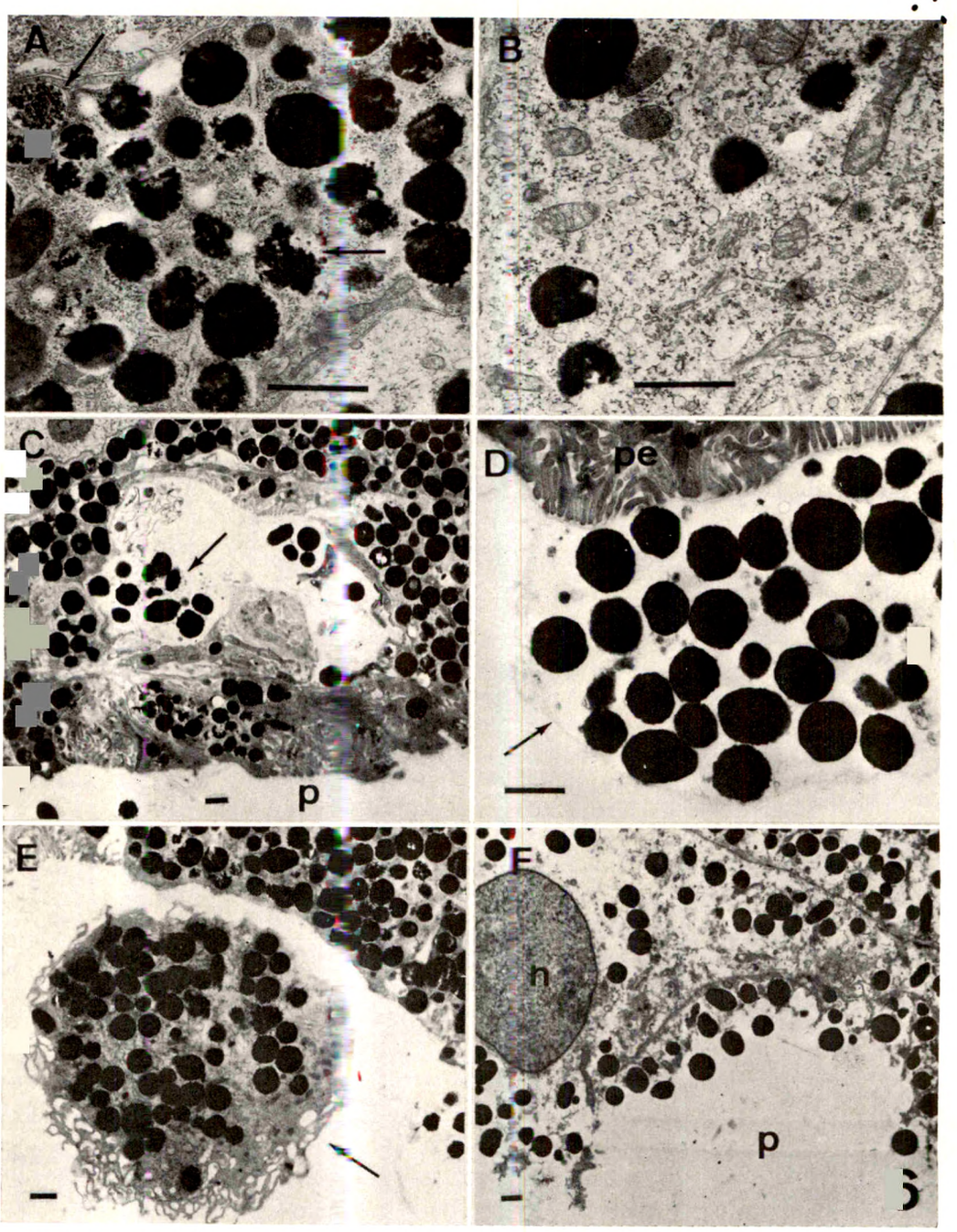



Fig. 6 (Iwamoto, Witmer, and Lambert). Various changes observed in the iris pigment epithelium. (A) Apparently degenerated pigment granules, many of which have lost their round shape, showing rugged surface. Some appear to be disrupted into irregular aggregates of smaller particles (arrows) (×14,700). (B) An area with sparsely distributed pigment granules (×14,700). (C) The cell in the center appears to have been completely degenerated, leaving cell debris and freed pigment granules (arrow). A few granules are in the posterior chamber (p) (×3500). (D) A group of freed pigment granules is surrounded by a membranous structure (arrow), and attached to the posterior surface of the iris pigment epithelium (pe) (×8700). (E) A cell (arrow) resembling the clump cell in the iris stroma is located in the posterior chamber near the iris pigment epithelium (upper portion). This cell may be a pigment epithelial cell released from the epithelial layer (×3750). (F) Most portions of the pigment epithelial cells facing the posterior chamber (p) appear to have been lost. Remaining epithelial cells have degenerative cytoplasms (×3,060).

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OPHTHALMIC MINIATURE

It is said in Aristotle's *Master Piece,* "That when a man doth think of anything which is past, he looketh down upon the ground; but that when he thinketh of something which is to come, he looketh up towards the heavens.

My uncle Toby, I suppose, thought o' neither—for he looked horizontally.

Lawrence Sterne
*Tristram Shandy,* 1760

# PATHOPHYSIOLOGY OF THE DISTAL PORTION OF THE OPTIC NERVE
## IV. Local Temperature as a Measure of Blood Flow

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During the past several years there has been a concentrated effort to obtain experimental evidence which would elucidate the pathogenesis of glaucomatous optic nerve disease. It has been shown that there is a decrease in vascularity of the optic disk in glaucomatous eyes.[1-3] This decrease in vascularity of the papilla is believed to result from the elevated intraocular pressure.[4,5] Animal experiments have demonstrated that acute increases in the intraocular pressure result in vascular compromise of the distal portion of the optic nerve.[4,6] The retinal circulation, however, and more specifically the radial peripapillary capillaries of the retina,[7] are not affected by intraocular pressures which compromise the choroidal vasculature and its optic nerve branches.[5,8]

This study was undertaken to further analyze the changes in the vascularity of the distal portion of the optic nerve secondary to variations in the intraocular pressure.

### Materials and Methods

Eighteen adult cats, both male and female of mixed breeds, were used. The animals ranged in weight from 2.3 to 3.6 kg and they were anesthetized with sodium pentobarbital, 30 mg/kg administered intraperitoneally. The anesthesia was maintained by supplements of sodium pentobarbital administered intravenously. A tracheostomy was performed and the animal's breathing was assisted by a respirator (Harvard, model 672). The arterial blood pressure was monitored from a cannulated femoral artery with a pressure transducer (Statham, model P23AC) and recorded on one channel of a polygraph (Grass, model 5D).

A lateral canthotomy was done and the eye was stabilized and cannulated by the method we have previously described.[9] Briefly, it consisted of attaching a Flieringa ring to the globe and then using rods to support the ring. The intraocular pressure was regulated through an anterior chamber cannula connected to a saline reservoir by polyethylene tubing. A second pressure transducer whose output was recorded by another channel of the polygraph was inserted in the system to monitor the intraocular pressure levels.

A micromanipulator (Brinkmann, model RP-IV/L) was used to pass a 22-gauge thin-wall needle containing a trocar through the cornea and lens into the vitrous cavity. The trocar was then removed and a copper-constantan thermocouple inserted in its place. The experiment was in two parts. In Part I, actual temperature measurements were made inside the eye. In Part II, relative temperature measurements were made with both the sensor and its reference junction within the eye.

A 30-gauge thermocouple probe (Ultra-miniature Thermocouple Needle, High Temperature Instruments Corp.) was used for the actual temperature measurements in Part I of the study and for half of the relative measurements in Part II of the study. The cooper and constantan wires from the fused junction at the tip of the needle passed through a double-bore quartz tube. The quartz tube was housed within a 30-gauge needle. In Part I, actual temperature measurements were obtained by directing the needle through the eye and into the optic

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disk. The reference junction was placed in refluxing dichloromethane. The boiling point of dichloromethane, dependent on the atmospheric pressure, is approximately 40°C. The temperature was measured to the nearest 0.1°C with a liquid-in-glass thermometer.

In Part II, the reference junction was placed inside the eye and relative temperature measurements were obtained. The cannula through the cornea and lens into the vitreous was increased in diameter to 19-gauge and two techniques of relative temperature measurement were employed. In the first technique, two of the needle probes described above were inserted into the eye. The two junctions were connected in series so that the probes referenced each other. A series of measurements were obtained with one probe in the vitreous cavity and the second probe on the optic disk. Another series of measurements were made with one junction on the optic disk and the other pushed into the nerve substance posterior to the lamina cribrosa.

In the second technique of relative temperature measurement a specially designed twin junction probe was used (Differential Temperature Probe, High Temperature Instruments Corp.). The copper and constantan wires of each fused junction passed through double-bore quartz tubes as described above for the single probes. However, there were two such double-bore tubes placed within an outer quartz envelope (Fig. 1). This quartz envelope was then cemented inside a 23-gauge stainless steel needle. The assembled probe is illustrated at the bottom of Figure 1. The first junction was placed at the tip of the probe and connected in series with the second junction which was fixed 2 mm behind it.

The EMFs produced by temperature differences between junctions were amplified in each case by a microvoltmeter (Keithley, model 150B) and recorded by the polygraph.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

## Results

*Part I, temperature measurements*—The reference junction for the 30-gauge thermocouple probe was placed in boiling dichloromethane. EMF measurements were then made for air 1 cm in front of the eye, on the cornea, in mid-vitreous, on the optic disk, and in the nerve substance posterior to the lamina cribrosa. In Table 1 measurements from three animals are recorded. The EMF-temperature conversion was made on the basis of the slope of a standard curve at 40°C.[9] This approximation is 42 microvolts per degree centigrade. It is important to note that in all three experiments there is a 0.1°C temperature increase across the lamina cribrosa.

Following the temperature determinations across the eye, the thermocouple was placed on the optic disk and the intraocular pressure elevated and maintained above the systemic systolic blood pressure. Figure 2 is a

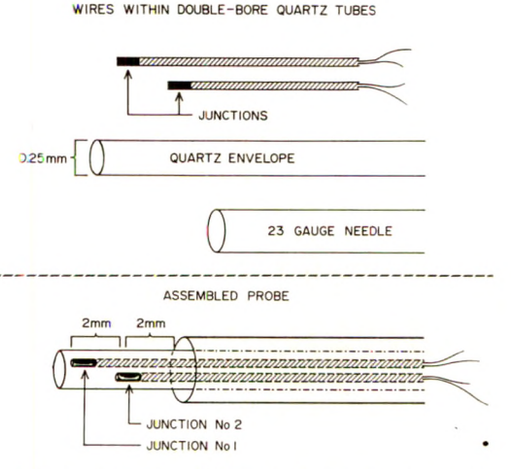



Fig. 1 (Ernest and Potts). Drawing of the differential temperature probe showing the positions of the two copper-constantan thermo-elements (U.S. Army photograph).

TABLE 1

TEMPERATURE MEASUREMENTS
(degrees centigrade)

| Cat No. | Body | Air | Cornea | Vitreous Cavity | Optic Disk | Optic Nerve |
|---|---|---|---|---|---|---|
| 610 | 38.3 | 21.0 | 29.9 | 36.7 | 37.6 | 37.7 |
| 616 | 38.9 | 21.4 | 29.7 | 36.0 | 37.6 | 37.7 |
| 619 | 40.0 | 21.2 | 30.0 | 36.1 | 37.7 | 37.8 |

photograph of the polygraph record obtained from one such experiment. The temperature decreased from approximately 37.7 to 36.4°C over a period of approximately two minutes.

*Part II, differential temperature measurements*—Differential temperature measurements were obtained by two methods. In the first method, two 30-gauge thermocouple probes were inserted into the eye. One needle junction was placed on the optic disk and the second needle junction pulled back 2 mm into the vitreous cavity. The intraocular pressure was then acutely elevated to approximately the level of the systemic diastolic blood

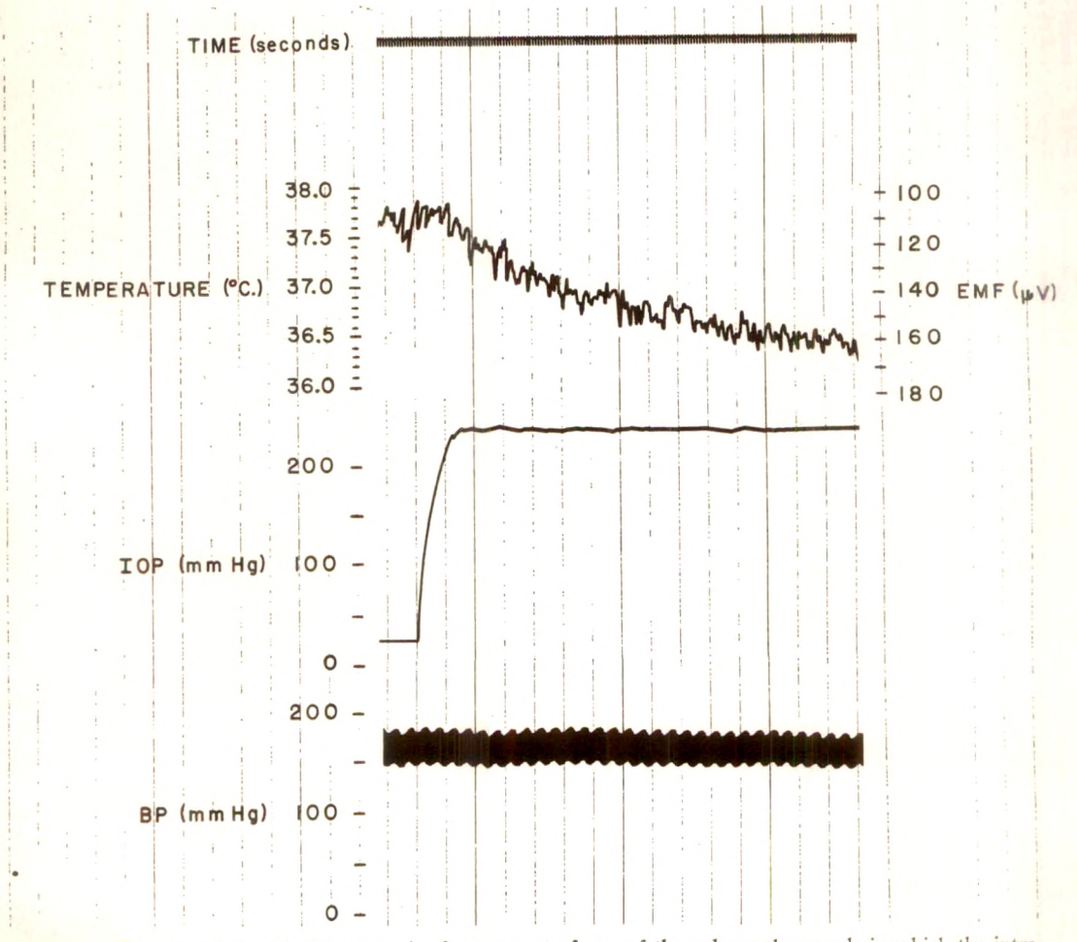



Fig. 2 (Ernest and Potts). Photograph of a segment of one of the polygraph records in which the intraocular pressure was raised above the level of the systemic systolic blood pressure (U.S. Army photograph).

pressure. This resulted in a relative decrease in the temperature of the sensor on the optic disk relative to the sensor in the vitreous cavity (Fig. 3-a). The position of the probe was then changed. The first sensor which had been on the optic disk was pushed through the lamina cribrosa into the nerve substance. The second sensor which had been in the vitreous cavity was placed on the optic disk. The intraocular pressure was again elevated resulting in a relative cooling of the second sensor which was now on the optic disk (Fig. 3-b).

In the second method used to make differential temperature measurements, the specially constructed two-junction probe was inserted into the eye. Junction No. 1 of the probe was placed on the optic disk and the intraocular pressure elevated to approximately 90 mm Hg. This level is considerably below the systemic diastolic blood pressure. Figure 4 is a photograph of one of the polygraph records from this series of experiments. The temperature of junction No. 1 on the optic disk decreased 0.08°C and then started a slow recovery. When the intraocular pressure was normalized, there was an overshoot followed by a slow return to initial levels. The overshoot means that for approximately 15 seconds the optic disk was warmer than control levels.

In the final series of experiments the differential probe was used but a bias voltage was added to the circuit so that the microvoltmeter could be set to a high gain of 3 microvolts, full scale. During brief periods of both temperature and electrical stabilization, it was possible to measure the effect of minimal variations in the intraocular pressure. Figure 5 is a photograph of a segment of one of the polygraph records from this series of experiments. The intraocular pressure was leveled at 17.5 mm Hg and when the temperature became stable, the intraocular pressure was raised 10 mm Hg. It is evident from the record that there was a simultane-

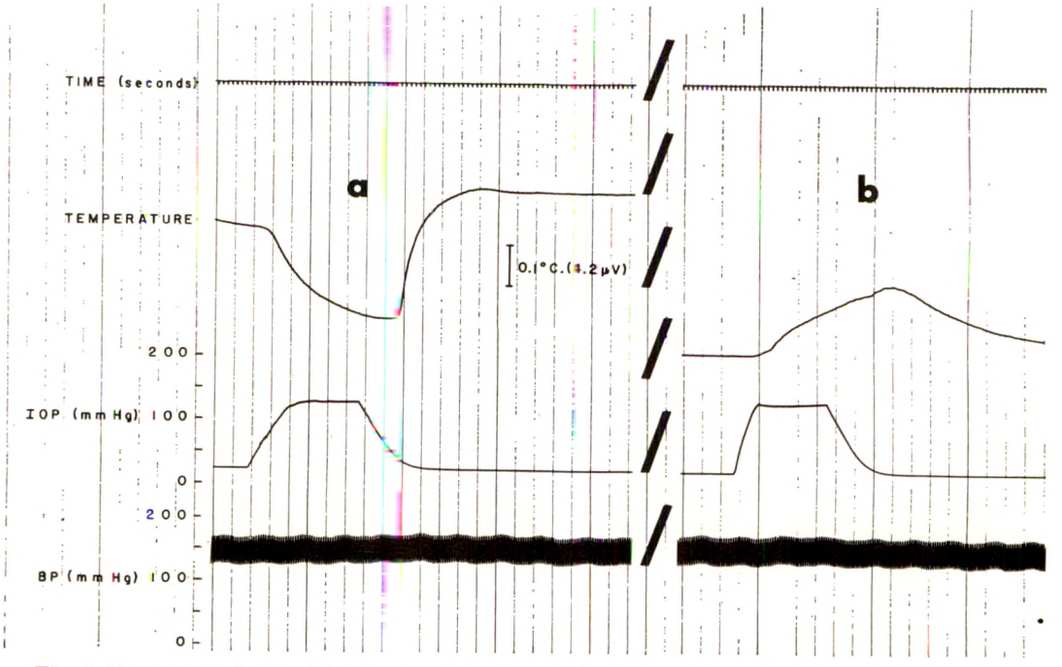



Fig. 3 (Ernest and Potts). Photograph of two segments of one of the polygraph records in which the intraocular pressure was elevated. In the first segment (a) one junction was on the optic disk and the reference was in the vitreous. In the second segment (b) the reference junction was on the optic disk and the other junction 2 mm posterior to the lamina cribrosa (U.S. Army photograph).

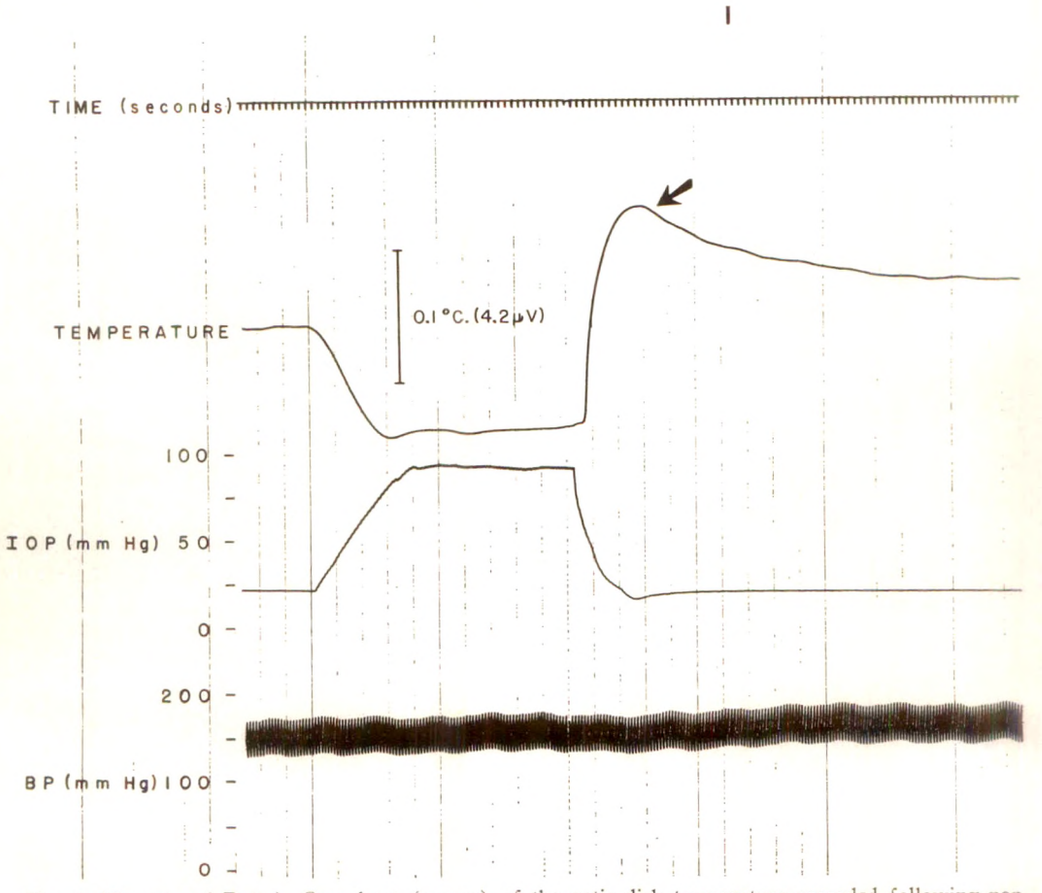



Fig. 4 (Ernest and Potts). Overshoot (arrow) of the optic disk temperature recorded following normalization of an elevated intraocular pressure (U.S. Army photograph).

ous decrease in the temperature of the optic disk. At the end of approximately one minute the pressure was returned to its original level and the optic disk temperature returned to slightly higher than its base line level. Experiments were also carried out in the opposite direction. Following several minutes with the intraocular pressure leveled at 17.5 mm Hg, it was decreased 5 mm Hg. This resulted in a transient increase in the temperature of the optic disk.

## Discussion

With the cornea exposed to the air the globe constantly lost heat. The methods of heat loss from the various eye tissues and the resulting heat gradient are illustrated in Figure 6. Since the blood, heated by the metabolic processes of the entire body, is the source of heat, the highly vascularized posterior segment has the highest temperature. Schwartz and Feller[11] have shown that the optic disk is at a higher temperature than the vitreous. The highest temperature we recorded was in the nerve substance 2 mm posterior to the lamina cribrosa. The amount of heat produced by the tissue of the disk itself is negligible in comparison with the heat conveyed to the disk by the arterial blood. The heat is transferred by conduction through the vitreous, lens, and aqueous to the cornea. The small amount of heat radiated by the optic disk due to its temperature of approximately 310° Kelvin is in the infrared region of the electromagnetic spectrum. It is thus absorbed by the high water

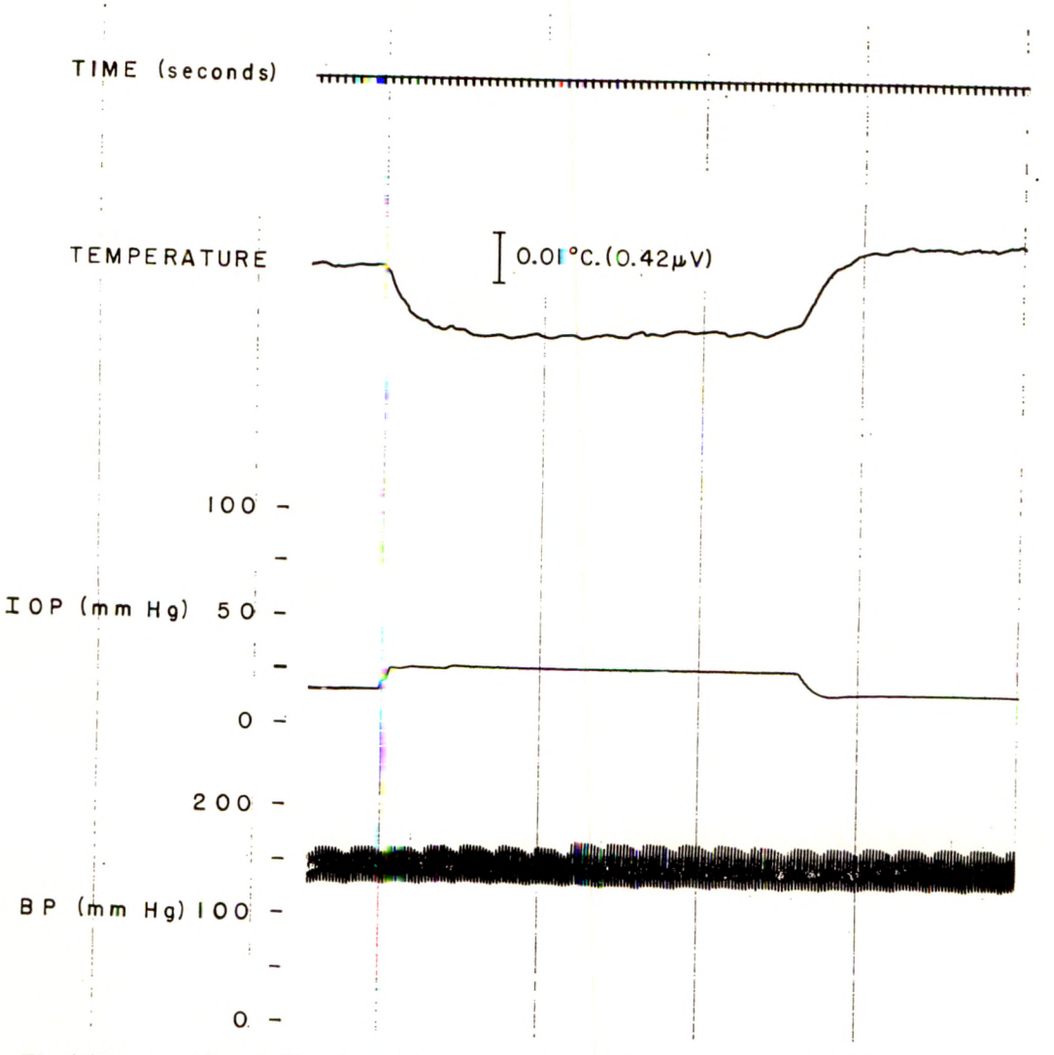



Fig. 5 (Ernest and Potts). The microvoltmeter was adjusted for the maximum amplification possible while still maintaining an acceptable signal-to-noise ratio. This made it possible to record the optic disk temperature decrease which accompanied a 10 mm Hg increase in the intraocular pressure (U.S. Army photograph).

content of the ocular media. The transfer of heat through the aqueous is due to convection as well as conduction. The heat transfer by convection is due partly to aqueous flow in an anterior direction and partly to thermal circulation within the aqueous.

The cornea's heat loss to the atmosphere is the reason for the heat gradient within the eye. When the eyelids are closed so that heat is not transfered from the cornea, there is no longer a heat gradient within the eye.[12] The cornea, like all bodies at a higher temperature than their environment, loses heat by radiation, conduction and convection. Further, because of tear film evaporation, the cornea is also cooled by vaporization. Mishima[13] and Iwata and associates[14] have shown that there is an evaporation of between 2.2 and 3.7 μl/hour/cm$^2$ of cornea. The heat of vaporization of water is 0.54 calories/mg or μl. Thus the cornea loses approximately 1.5 calories/hour by vaporization. If we assume that the

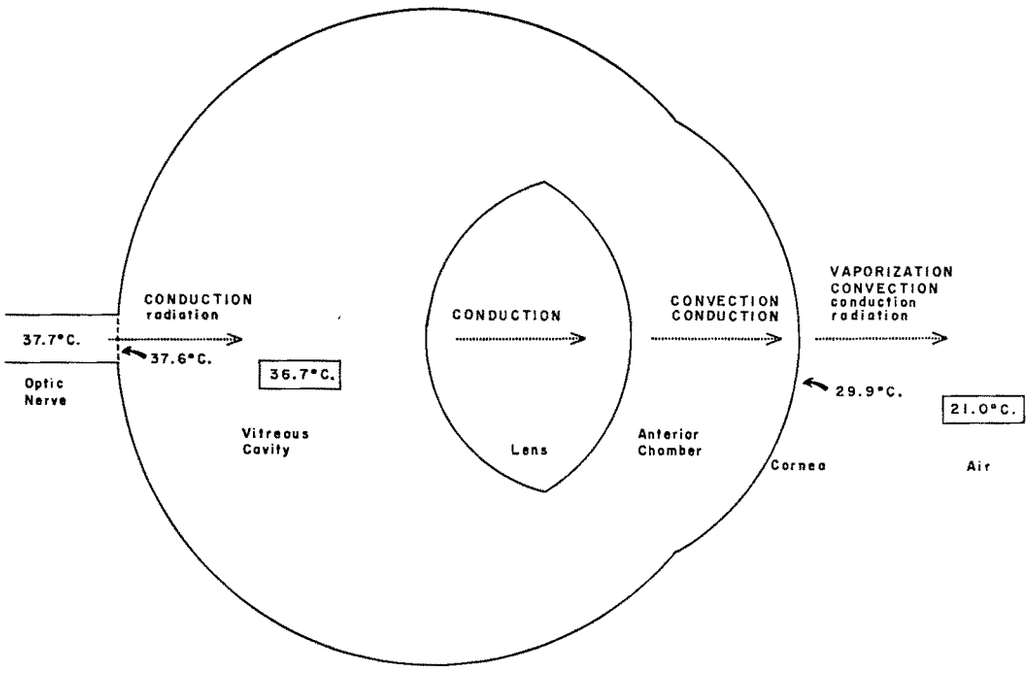



Fig. 6 (Ernest and Potts). Illustration of the temperature gradient within the eye (U.S. Army photograph).

cornea is a blackbody, then the rate of heat loss by radiation is proportional to the area and the fourth power of the absolute temperature (Stefan-Boltzmann law). For the case of small temperature differences, however, the rate of cooling is proportional to the difference in temperature between the cornea and its surroundings. Further, the net rate at which the cornea loses heat by radiation depends on the difference between the rate it receives radiant energy and the rate at which it loses radiant energy, and thus the resultant is variable and of an insignificant magnitude. The transfer functions for convection losses are complicated since they depend on both the conduction of heat into the air in contact with the tear film and the motion of this air. The loss of heat from the cornea to the air by conduction is of small magnitude since the thermal conductivity of air is negligible. The movement of the air in contact with the tear film is obviously variable. In our experiment we tried to minimize air movement so that the only convection currents were natural ones. During normal awake activity with continual blinking, however, heat exchange by forced convection may become a major source of corneal heat loss.

The optic disk temperature depends on two factors. First, the rate of heat brought to it by the blood and second, its rate of heat loss into the eye. If either of these factors is altered, the temperature of the optic disk will change. In our experiment the rate of heat loss was held constant. Thus the changes observed in the optic disk temperature were due to changes in the amount of heat brought to the disk by the blood. The temperature of the blood was constant during the experiment. Therefore, changes in the temperature of the optic disk were due to alterations in blood flow (volume/unit time). There were either changes in the blood volume of the vasculature of the optic disk, changes in the rate of blood flow or a combination of both. It was not possible to determine if only one or both of these parameters was changing.

Further, although the EMF of the thermocouple we used was linear over the range of temperatures measured, it does not mean that there was a linear relationship between the temperature of the optic disk and changes in its blood flow. Nonetheless it was possible to make a qualitative assessment of the blood flow of the optic disk. The records (Figs. 2 through 5) show that the systemic arterial blood pressure remained constant. If it is assumed that the systemic venous blood pressure remained constant, then the decrease in temperature caused by an increase in intraocular pressure must have been due to a mechanical interference with the optic disk circulation. The fall in the temperature of the optic disk when the intraocular pressure was elevated to a level above the systemic systolic blood pressure (Fig. 2) was fitted well by an exponential curve of the form ($y = e^{-ax}$). The $a$, which reflects the rate of temperature decay, was 0.02. This exponential decrease in optic disk temperature from 37.7 to 36.4°C represents the maximum driving force available for our probe temperature measurements over the time periods studied.

A possible source of error in the optic disk temperature measurements was the relative movement of the probe when the intraocular pressure was elevated. With an increase in the intraocular pressure, the internal diameter of the globe enlarged due to compression of the uveal tissue. The probe, however, was not fixed to the globe and so moved slightly with respect to the optic disk. To determine the effect of this change in position of the probe with respect to the disk tissue, the following experiment was performed. The intraocular pressure was maintained at a constant level and the probe was moved up mechanically an amount approximating its relative movement when the intraocular pressure was maximally elevated. The result was a rise of approximately 1% in the recorded temperature. Since this temperature change was small and in a direction opposite to that observed when the intraocular pressure was increased, the movement of the probe relative to the optic disk was considered negligible.

The primary problem was to measure the small changes in temperature associated with minimal alterations in the intraocular pressure. For this purpose, we placed the reference junction physically close to the measuring junction of the probe. The advantage of this technique was that the sensitivity to temperature change was greatly increased. With the junctions at approximately the same temperature, both the EMF generated and the bias required to balance it, were low. Consequently, the electrical noise was minimal and the relative "gain" of the amplifier could be markedly increased. It is important to note however, that when the reference junction was placed within the eye, only transient changes in the intraocular pressure could be studied. Following an increase in the intraocular pressure and the resultant fall in optic disk temperature, the new lower temperature level gradually cooled the reference junction. Thus the original temperature gradient was restored and the EMF returned to the initial level even though the intraocular pressure elevation was maintained.

The probes were placed in contact with the center of the optic disk. The diameter of the cat's optic disk is approximately 1 mm. Nonetheless, the thermocouples could have been monitoring peripapillary temperature changes as well as changes occurring in the distal segment of the optic nerve. To make certain this was not the case, the temperature sensor was placed in several locations on the peripapillary retina and the intraocular pressure elevated. The resulting temperature changes differed in three ways from those occurring when the probe was in contact with the center of the optic disk. First, for the same increment increase in the intraocular pressure, the percentage temperature decrease was less when the probe was in contact with the peripapillary retina than when it was in contact with the optic disk. If the optic disk was acting as a heat sink for the

peripapillary retina and choroid, the percentage changes would be approximately equal. Second, the latencies between the time the intraocular pressure was increased and the temperature decreased were exactly the same whether the probe was on the optic disk or the retina. If the optic disk was only reflecting temperature changes of the retina and choroid, there would be a relative delay in its temperature change with an increase in the intraocular pressure. Third, there was only a small overshoot of the peripapillary retinal temperature when the intraocular pressure was normalized while the overshoot of the optic disk temperature was a minimum of three times greater.

The use of the two separate thermocouple probes made it possible to compare changes in blood flow in the optic disk across the lamina cribrosa. Elevation of the intraocular pressure caused a decrease in blood flow of the optic disk (Fig. 3-a). When the probe was pushed through the lamina cribrosa and the reference junction moved on to the disk, the decrease in blood flow with an elevation in the intraocular pressure again occurred at the disk resulting in a reversal of the temperature curve (Fig. 3-b). The junction which had been in the vitreous and consequently unaffected by a change in optic disk blood flow the first time was now on the optic disk. It was thus cooled by a decrease in blood flow with the elevation in the intraocular pressure. The junction which had been on the optic disk was now in the distal segment of the optic nerve posterior to the lamina cribrosa surrounded by vessels which were not directly affected by the elevation in the intraocular pressure. We have previously shown that the intraocular pressure is not transmitted posterior to the lamina cribrosa.[9] When the reference junction is posterior to the lamina cribrosa, however, temperature changes with alterations in the intraocular pressure were slower and of a smaller amplitude than those measured with the reference junction in the vitreous. This means that there was a slight decrease in temperature of the region posterior to the lamina cribrosa during the periods of intraocular pressure elevation. There are two possible explanations for this. First, the intraocular pressure has an effect posterior to the lamina cribrosa. We have previously shown that this is not the case even when a 30-gauge cannula is in place through the lamina cribrosa.[9] Second, the source of blood for the nerve substance immediately posterior to the lamina cribrosa is the intraocular vasculature which is subjected to the intraocular pressure. Thus, when the intraocular pressure was elevated and the blood flow of the optic disk was compromised there was also a relative decrease in the blood flow and thus the temperature of the nerve substance posterior to the lamina cribrosa. This would also account for earlier findings obtained by contrast material injection experiments.[4,6] When the intraocular pressure was elevated and contrast material was injected into the ocular vasculature, both the optic disk vessels and a variable segment of the optic nerve immediately posterior to the lamina cribrosa showed a filling defect.

To obtain the maximum sensitivity possible, the differential thermocouple with its fixed probe and reference junctions was used. When the intraocular pressure was returned to base line levels following elevations of approximately 90 mm Hg, there was a transient overshoot of the blood flow in the optic disk above control levels (Fig. 4 arrow). Bill[15] has shown that there is a reactive hyperemia of the uveal blood flow following periods of increased intraocular pressure. Why there should be a reactive hyperemia following normalization of the intraocular pressure is not clear. Whether there is a depletion of oxygen in the optic disk tissue with a resultant effect on the vasculature is under study at this time.

In the final series of experiments we demonstrated that an increase in the intraocular pressure of as little as 10 mm Hg caused a decrease in the optic disk blood flow (Fig. 5). For the reasons discussed above, it could not be determined if the optic disk

blood flow eventually compensated for small increases in the intraocular pressure. It is significant, however, that intraocular pressures which are definitely in the physiological range, decrease the optic disk blood flow. Further, this is the first demonstration that changes in the intraocular pressure of the order of magnitude of those seen in chronic open angle glaucoma in man, do indeed decrease the blood flow in the optic disk.

## Summary

Thermocouple probes with maximum diameters of 0.3 mm have been used to measure the temperature changes in the distal segment of the optic nerve of the cat secondary to changes in the intraocular pressure. With all thermal factors (ambient temperature, body temperature, evaporation rate from eye) held constant, small changes in blood flow are detectable as changes in temperature at the thermocouple tip.

Using this system, small elevations in intraocular pressure—well within the range of the elevations found in open angle glaucoma—cause measureable decrease in blood flow as reflected by decrease in temperature.

Conversely, in our experimental system, normalization of the intraocular pressure after relatively large elevations of pressure results in hyperemia of the nerve head and a corresponding temperature increase.

### Acknowledgment

We acknowledge the technical assistance of Specialist-7 Joseph Fritz.

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# RESISTANCE TO AQUEOUS OUTFLOW IN THE RHESUS MONKEY EYE

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On the basis of current evidence, it is generally held that in human eyes the primary site of resistance to aqueous outflow lies in the trabecular meshwork. In monkey eyes, however, results of investigations attempting to localize the site of maximal resistance have prompted varied conclusions. The present work, utilizing Grant's experimental approach in enucleated human eyes,[1,2] was therefore undertaken to gain further information on the resistance offered by the various portions of the aqueous outflow pathway in enucleated rhesus monkey eyes, information which would be closely comparable with that previously obtained in human eyes.

## MATERIALS AND METHODS

Experiments were done on 50 ostensibly normal adult rhesus monkey eyes which were enucleated at sacrifice, stored in a cool, moist chamber, and used within two days postmortem. Determinations of facility and resistance were made using the constant pressure perfusion method of Grant.[1,2] A 5.0 mm trephine hole was made in the cornea and, after a radial iridotomy was made to prevent artificial deepening of the anterior chamber, the eye was connected to the perfusion-recording system by means of a stainless steel fitting. Perfusion was done at room temperature using 0.9% saline.

In order to assess the degree of resistance offered by different portions of the aqueous outflow pathway, perfusion was carried out before and after certain dissections done under the Zeiss operating microscope:

A. To study the resistance offered by the outermost portions of the outflow channels, 10 eyes were initially perfused with 5-6 mm of perilimbal conjunctiva remaining, with 10-12 mm of recti muscles attached, and with subconjunctival and episcleral tissues present (baseline). After steady state was attained, the conjunctiva was cut away close to the limbus, the muscles cut at their scleral insertions, and the subconjunctival and excess episcleral tissues removed in 360 degrees leaving only a very thin layer of episclera containing blood vessels. The eyes were then reperfused and changes in facility and resistance determined.

B. To assess the resistance offered by the portions of the aqueous outflow pathway in the outer sclera, 10 eyes were initially perfused as described above and then reperfused after the outer one-half to two-thirds of the perilimbal sclera over Schlemm's canal had been shaved away in 360 degrees.

C. To determine the resistance to aqueous outflow presented by the trabecular meshwork, 28 eyes were perfused before and after trabeculotomy was done over 5% (four eyes), 25% (eight eyes), 50% (six eyes), and 100% (10 eyes) of the total circumference. Two of the 5% trabeculotomies were done in the superior quadrant and two in the lateral quadrant, whereas four of the 25% trabeculotomies were done in the superior quadrant and four in the medial quadrant. All six of the 50% trabeculotomies were over both superior and medial quadrants. Trabeculotomy was accomplished directly through the corneal trephine opening using a Sato corneal knife.

At the conclusion of each experiment, perfusion with fluorescein-tinted fluid was carried out under black light in order to study the patterns of aqueous outflow from the

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eye. Specimens were then fixed in formaldehyde, embedded in paraffin, sectioned anteroposteriorly at regular intervals, stained, and examined microscopically. Where trabeculotomy was done in only a part of the circumference, sections were cut to include both operated and nonoperated angle on the same slide.

Analysis of the data and plotting of the graphs by standard statistical techniques were carried out using an IBM 7094/7040 direct coupled computer system.

## Results

Control perfusions were carried out in six eyes to evaluate the effects of cold storage, artificial manipulation, and removal and reinsertion of the corneal adapter. In one eye the measured facility value increased by 0.02 μl/minute/mm Hg, in two eyes it decreased by 0.01 μl/minute/mm Hg, and in three eyes the facility did not change.

The results of the experiments of series A are presented in part A of Table 1. The portions of the outflow channels in the conjunctiva, episclera, and proximal extraocular muscles accounted for very little, if any, of the outflow resistance under the experimental conditions.

In the experiments of series B, the operative procedure resulted in a moderately deep circumferential perilimbal scleral defect, in the depths of which could be seen some of the exiting aqueous channels in cut cross-section. Fluorescein perfusion showed colored fluid to exit only from about 20 such cut vessels, and there was no evidence that Schlemm's canal had accidentally been exteriorized. Histologic study of these eyes revealed that the operation had removed the outer one-half to two-thirds of the sclera over Schlemm's canal. The results of facility and resistance determinations in these experiments, tabulated in part B of Table 1, show that approximately 10-15% of the outflow resistance can be localized to the outer sclera removed.

For the trabeculotomies of series C, a surgically satisfactory view of the angle was obtained without abnormal depression of the iris (Fig. 1). The knife tip, which presented no scleral cutting edge, was positioned without difficulty and incision into the trabecular wall of Schlemm's canal was done with relative ease. Different eyes showed variations in their resistance to the actual cutting of the meshwork, however. Where trabeculotomy was done, the glisten-

TABLE 1

EFFECTS OF (A) REMOVING THE CONJUNCTIVA, SUBCONJUNCTIVA, EPISCLERA, AND RECTI MUSCLES; (B) OF REMOVING THE OUTER ONE-HALF TO TWO-THIRDS OF THE PERILIMBAL SCLERA; AND (C) OF TRABECULOTOMY IN VARYING FRACTIONS OF THE CIRCUMFERENCE ON THE FACILITY OF AND RESISTANCE TO AQUEOUS OUTFLOW IN ENUCLEATED RHESUS MONKEY EYES
(mean ± s.e.m.)

| Procedure | (n) | Facility (μl/min/mm Hg) | | Resistance (mm Hg/minute $^{-1}$/μl) | | | P* |
|---|---|---|---|---|---|---|---|
| | | Baseline | Postoperative | Baseline | Postoperative | Change | |
| A | 10 | 0.59±0.04 | 0.58±0.04 | 1.80±0.15 | 1.84±0.15 | + 2±3% | >0.5 |
| B | 10 | 0.54±0.06 | 0.63±0.08 | 2.10±0.26 | 1.89±0.29 | −12±3% | <0.01 |
| C 5% | 4 | 0.33±0.01 | 0.54±0.05 | 3.70±0.11 | 1.90±0.12 | −38±5% | <0.002 |
| 25% | 8 | 0.55±0.05 | 1.25±0.17 | 1.96±0.17 | 0.92±0.16 | −51±8% | <0.01 |
| 50% | 6 | 0.53±0.03 | 1.03±0.12 | 1.91±0.10 | 1.04±0.12 | −46±4% | <0.01 |
| 100% | 10 | 0.51±0.05 | 1.52±0.19 | 2.11±0.19 | 0.81±0.11 | −63±4% | <0.001 |

* Student's t-test performed on paired differences between baseline and postoperative facility values or resistance values.

ing white scleral wall of the canal, bordered by trabecular fragments superiorly and inferiorly, became clearly visible (Fig. 2). This was particularly evident when the edges of the incision were spread slightly apart during the operative procedure. Even in a completely relaxed state, however, the lips of the incision generally did not appear to close. Grossly, no cyclodialysis resulted from these operations.

The results of this third series of experiments are summarized in part C of Table 1. In every case trabeculotomy was followed by a significant decrease in resistance (increase in facility), and the data suggest that the trabecular meshwork as a whole accounts for about 60-65% of the total resistance to aqueous outflow. A great similarity between the two eyes of any given animal was found, both in the initial facility and in the percent of decrease in resistance following the same degree of trabeculotomy. When either 5% or 25% trabeculotomy was done in different quadrants, no significant differences were observed in the mean decrease in resistance following the same percentage of trabeculotomy.

Observations of fluorescein perfusion of trabeculotomized eyes were rather variable, and clear-cut patterns were difficult to identify. Earliest and greatest outflow of colored fluid, however, was not always observed to be through aqueous veins draining the quadrants in which trabeculotomy had been done, although such a pattern was encountered about half of the time. Moreover, outflow was most often earliest and greatest in the superior, inferior, and (to a somewhat lesser extent) medial quadrants, irrespective of the site or extent of trabeculotomy. Flow through aqueous veins in the lateral quadrant was invariably slight. From 30-45 minutes after the start of fluorescein perfusion, by which time aqueous veins of all quadrants were draining fluorescein, examination through several equatorial scleral windows revealed no fluorescence in the suprachoroid to indicate the presence of a cyclodialysis. Also, no colored fluid was seen to exit from any of the vortex veins.

Microscopic examination of sections of the angle (Fig. 3) revealed that the trabecular meshwork had been successfully opened or removed in those areas operated upon. No histologic evidence of damage to the scleral wall of Schlemm's canal was found, the endothelial lining appearing to be intact, and

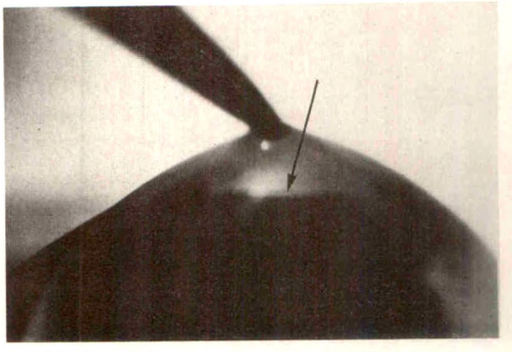


Fig. 2 (Peterson, Jocson, and Sears). Microscopic view of anterior chamber angle of rhesus monkey eye after trabeculotomy in 25% of the circumference (superior quadrant). Note the narrow, glistening white area within the trabecular band, representing the exposed scleral wall of Schlemm's canal (arrow), bordered by grey trabecular tissue anteriorly and posteriorly (×11).

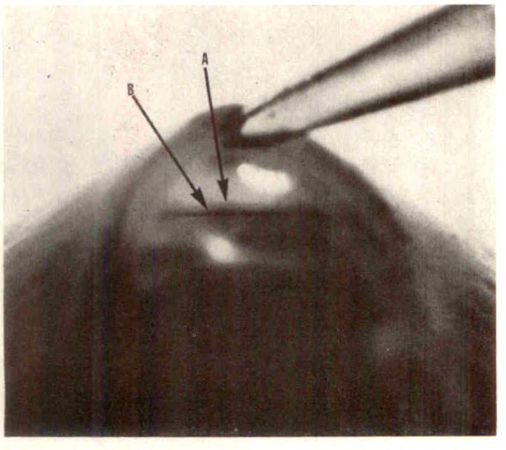



Fig. 1 (Peterson, Jocson, and Sears). Microscopic view of normal anterior chamber angle of rhesus monkey eye through a corneal trephine opening. Note grey, ground-glass appearance of trabecular band (A) overlying deeply pigmented ciliary body band (B). Schwalbe's line and scleral spur are not well defined (×11).

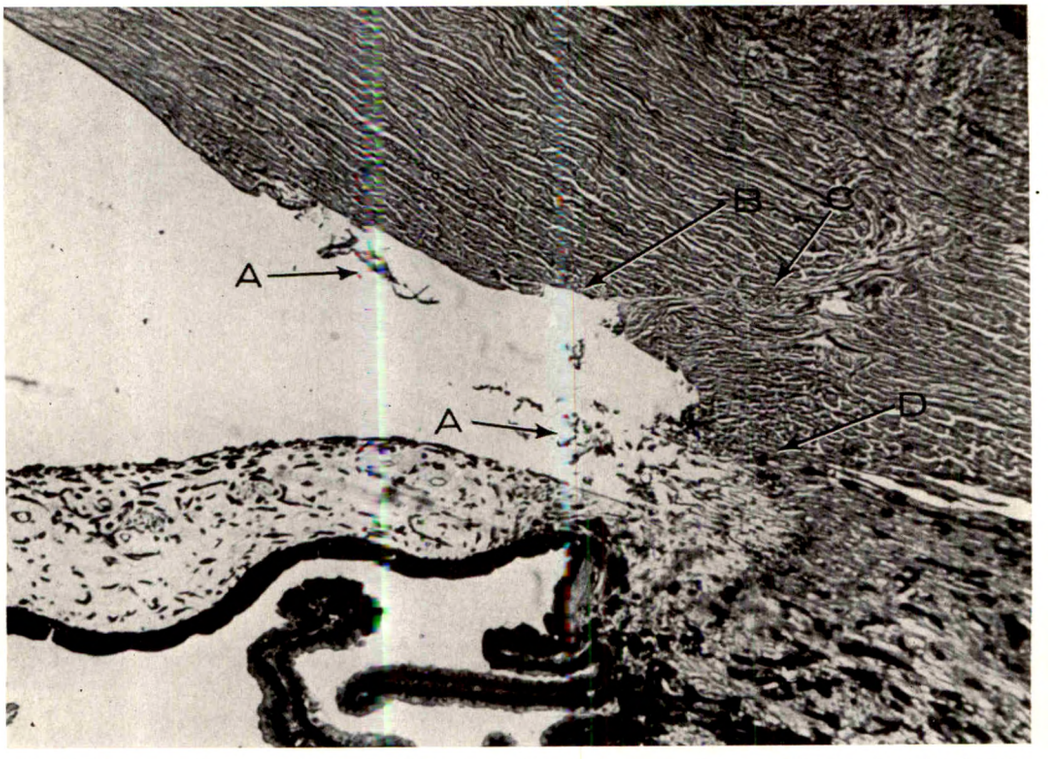



Fig. 3 (Peterson, Jocson, and Sears). Histologic section of rhesus monkey eye after opening of trabecular meshwork overlying Schlemm's canal. Note trabecular fragments anteriorly and posteriorly (A), integrity of endothelium lining scleral wall of Schlemm's canal (B), large exiting aqueous collector channel in sclera (C), and absence of a cyclodialysis (D) (hematoxylin-eosin, ×540).

no microscopic evidence of cyclodialysis was seen.

## Comment

The findings that very little resistance to aqueous outflow can be localized to the aqueous channels in the conjunctiva, subconjunctiva, episclera, and recti muscles, and that only 10-15% of the outflow resistance can be accounted for by the outer one-half to two-thirds of the perilimbal sclera, point out that the site of maximal resistance to outflow in the normal enucleated rhesus monkey eye must reside either in the deeper intrascleral portions of the aqueous outflow vessels or in the region of the trabecular meshwork. That the trabecular meshwork is in fact responsible for the principal resistance is indicated by the consistent results of the trabeculotomy experiments, which showed that 60-65% of the total resistance to outflow is accounted for by this structure. As regards the remaining 25% of the resistance, this must reside within the inner one-third to one-half of the sclera, either principally at the ostia of the collector channels directly draining Schlemm's canal or distributed along the many intrascleral vessels of the collecting system. Which possibility is more nearly correct is impossible to state, though the finding of a small but significant resistance in the outer sclera suggests the latter.

Gross and microscopic observations supporting the actual accomplishment of trabeculotomy without damage to the scleral wall of Schlemm's canal and without cyclodialysis have been presented. While it is probably impossible absolutely to exclude microscopic trauma to the outer wall of the canal, as serial sectioning was not done, it is just as dif-

ficult to conceive how such minute damage, not evident in any of the representative sections, could lead to the extensive increases in facility observed. It would also seem that such damage would be of variable nature and extent from eye to eye and hence unlikely to produce the consistent results in paired fellow eyes such as we have observed.

As seen in part C of Table 1, there is a distinctly nonlinear relationship between the percent of trabeculotomy and the percent of resistance removed, the mean percent of decrease in resistance after trabeculotomy in only a fraction of the circumference being greater than that which would be expected if the relationship were linear. Thus it is apparent that a relatively small initial opening into Schlemm's canal increases the facility of outflow proportionally much more than does subsequent extension of the incision. This observation could mean that there is circumferential flow in Schlemm's canal, but other interpretations cannot be excluded.

The results of the fluorescein perfusions in the present study lend some support to this conclusion, for if no circumferential flow occurred then the fluorescein outflow would have been consistently greatest from the trabeculotomized quadrants where resistance was least. On the contrary, earlier and augmented flow of fluorescein most often came from superior and inferior quadrants, regardless of the site or extent of trabeculotomy. This observation is consistent with anatomical findings that in monkeys the collector channels draining Schlemm's canal in the superior and inferior quadrants are larger, are less intricately disposed, and exit more directly to the episclera than those in the medial and (especially) lateral quadrants (unpublished observations, V.L.J.).

The results of our experiments in rhesus monkey eyes, localizing the site of maximal resistance to aqueous outflow to the trabecular meshwork, are generally consistent with the previous studies in human eyes by Grant.[1,2] One may speculate that our slightly lower estimate of the total trabecular resistance (60-65% vs Grant's 75-80%), and our correspondingly higher estimate of the distal resistance, might be due in part to the differences in the anatomy of the intrascleral outflow vessels in the two species.[3,4] Species differences in the trabecular meshwork might also be an important consideration in this regard. Grant, however, observed greater outflow of perfusion fluid from the aqueous vessels draining the trabeculotomized quadrants more consistently than we did. This, plus his finding that "experimental opening into Schlemm's canal in only a fraction of the circumference does not increase facility of outflow as much as opening into the canal in the whole circumference," led Grant to the interpretation that "perfusion fluid . . . does not readily flow circumferentially in Schlemm's canal." Re-examination of Grant's original published data, however, reveals that in these experiments as in ours, trabeculotomy over a small portion of the circumference resulted in a greater decrease in resistance than would have been expected if the percent of decrease in resistance varied directly with the extent of trabeculotomy.

Our results are also compatible with the observation recently reported by Dannheim and Bárány[5] that trabeculotomy ab externo in four living rhesus monkeys, though generally not in cynomolgus monkeys, significantly lowered the resistence to aqueous outflow. Data from similar experiments reported by Edwards and associates[6] were quite variable and thus not conclusive.

The conclusions based upon the present experiments appear not to agree with those drawn by Perkins[7] and by one of us (M.L.S.)[8] from previous experiments in living monkey eyes. In these studies attempts were made to measure simultaneously, by direct manometry, the pressures in the anterior chamber and in the canal of Schlemm. The close similarity of these pressures was taken as evidence that the major resistance to outflow was located distal to the trabecular meshwork. It must be considered that exposure and cannulation of Schlemm's canal

from the outside are very difficult procedures and are likely to be complicated by injury to the very fragile trabecular meshwork, especially its lining endothelium. The large decreases in resistance which accompanied even small degrees of trabeculotomy in the present experiments suggest that such injury, however minute, might significantly reduce the resistance to aqueous outflow. Donnheim and Bárány[9] in fact found generally larger pressure differentials between the canal and the anterior chamber of monkey eyes than did these previously cited experimenters.

On the other hand, Schlemm's canal might normally be collapsed; in which case an otherwise poorly resistant trabecular wall, by virtue of its apposition to the scleral wall, would present an apparent high resistance to aqueous outflow.[8-10] It should be noted that Perkins[7] observed a marked increase in the rate of flow of saline into the anterior chamber after exteriorizing Schlemm's canal not only in one living and in one enucleated monkey eye but also in one enucleated human eye, observations suggesting that trabecular meshwork-scleral wall apposition might indeed be responsible for the primary resistance in both species. Our present data are not entirely inconsistent with this hypothesis, and experiments are in progress to test this speculation further.

The mean value for baseline facility of outflow in the rhesus eyes of this series is $0.52 \pm 0.02$ (50) µl/minute/mm Hg (mean $\pm$ s.e.m.) at room temperature of 24° C and at a mean experimental intraocular pressure of 8.0 mm Hg. Adjusting for the change in viscosity of the perfusion fluid with temperature, this becomes 0.73 µl/minute/mm Hg at rhesus body temperature of 38° C. The scatter of the values is typical of that observed in facility determinations in many species.[11]

An interesting finding was a rough but definite inverse variation, over the range of intraocular pressures observed (5.5-12.0 mm Hg), between facility of aqueous outflow and anterior chamber pressure at steady state (Fig. 4). Our value for rhesus monkey facility of outflow in vitro, when adjusted to a mean intraocular pressure of 12.5 mm Hg, thus becomes 0.40 µl/minute/mm Hg, a value comparable to the value of 0.41 µl/minute/mm Hg previously obtained in our laboratories[8] in eyes of living green monkeys under intravenous thiopental sodium anesthesia when mean intraocular pressure was 12.3 mm Hg. Examination of the data from this previous study also reveals an inverse relationship between facility of outflow and intraocular pressure as in the present study.

## Summary

Perfusion studies carried out in 50 enucleated normal rhesus monkey eyes suggested that the trabecular meshwork is responsible for 60-65% of the resistance to aqueous outflow, that aqueous outflow pathways in the inner one-third to one-half of the sclera are responsible for about 25%, that pathways in the outer one-half to two-thirds of the sclera account for 10-15%, and that more distal pathways account for very little, if any, resistance. An initial opening into Schlemm's canal increased the facility of outflow proportionally much more than did subsequent extension of the incision. Mean facility of aqueous outflow was found to be $0.52 \pm 0.02$

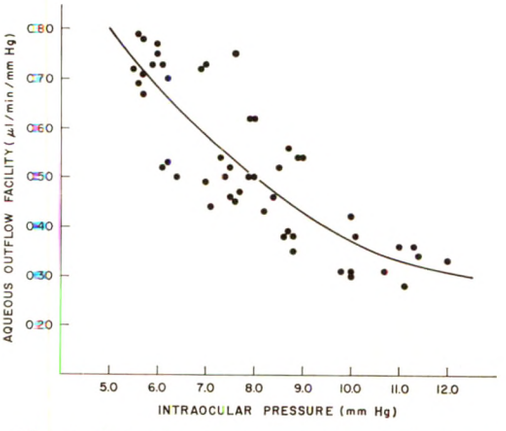



Fig. 4 (Peterson, Jocson, and Sears). Variation of aqueous outflow facility (µl/minute/mm Hg) with intraocular pressure (mm Hg) in 50 enucleated rhesus monkey eyes. Experimental values were determined at steady state, at room temperature, and in the baseline state described in the text.

(s.e.m.) μl/minute/mm Hg at body temperature and at a mean experimental intraocular pressure of 8.0 mm Hg. A rough but definite inverse variation of outflow facility with intraocular pressure was observed over the range of experimental intraocular pressures (5.5-12.0 mm Hg).

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## Ophthalmic miniature

At the lonely island of Salvagem Grande, Didi and I went down for our first dive. . . . We pushed off the ladder and immersed our masks. Simultaneously, with desperate reflex motions, we grabbed the ladder. We had glimpsed something which aroused a fear we had never experienced before. It was pure vertigo.

We exchanged glances and cautiously put our eyes under again, holding on to the ship. We saw the bottom 100 feet down in naked detail. There seemed no water below us. There were no motes of animals, plants, or minerals in the space. It was distilled water, not the benign speck-crammed element we call clear water, in which exceptional visibility embraced a space no bigger than a concert hall. We saw a horrible bright landscape. If we let go our handholds we thought we would plummet through empty space and crash on the malign rocks which ranged far across the floor.

At last we submerged and, suprisingly, the sea supported us. We swam down, seeing each other as gross, unfamiliar animals in that surgical water.

J. Y. Cousteau
*The Silent World*
London, Hamish Hamilton, 1953

# INTRASCLERAL SMOOTH MUSCLE IN COLOBOMA OF THE OPTIC DISK

## Electron Microscopic Verification

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*Washington, D.C.*

During the past several years, a group of congenitally malformed eyes has been the object of special interest and study because they have had in common the presence of bundles of elongated, spindle-shaped cells in the sclera and choroid along the edges of a colobomatous optic disk. Also, the optic nerves of these eyes are dysplastic, and their meningeal sheaths are incompletely formed or absent. In a number of them, masses of adipose tissue and bundles of plump, spindle-shaped cells are present within and about the optic nerve. Microscopic examination of sections stained by various methods for connective tissues and nerve fibers give the firm impression that the spindle-shaped elements found in the sclera, choroid, and optic nerve in these eyes are smooth muscle, but some pathologists who studied some of these cases in consultation were of the opinion that the cells in question might be schwannian. This paper reports electron microscopic studies that were carried out in one case to demonstrate more conclusively the nature of these cells.

### Case report*

A 13-year-old white girl was first examined in October, 1957, at the age of two to three months because of esotropia of her left eye. Examination revealed the right eye to be normal. The left eye was interpreted as highly myopic. A more thorough examination of the left fundus under general anesthesia with a well-dilated pupil revealed changes associated with high myopia, a posterior staphyloma, and a probable coloboma of the optic nerve. No definite mass was seen. In September, 1958, recession of the medial rectus and resection of the lateral rectus were performed for cosmetic improvement. At that time, examination of the left fundus under anesthesia showed a posterior staphyloma of some 25 to 30 diopters, with a "shot-silk" retina, underlying choroidal pigmentary changes, and some pallor of the superior nasal sector peripherally. No tumor was visualized. The right fundus was normal. The patient was re-examined in 1963, 1965, and 1967. She had no light perception with her left eye, and the appearance of her fundus remained unchanged. In April, 1969, uncorrected visual acuity in her right eye was 20/200, and she had no light perception in her left eye. In May, 1970, she had an "appendicitis attack," which cleared spontaneously and was followed by an infection of the urinary tract. Shortly thereafter, her left eye became red and painful, and she had tearing and swelling of both eyelids. Ophthalmologic examination two days later revealed corrected visual acuity in her right eye to be 20/20, with no light perception in her left eye, which was congested, with a steamy cornea and an irregular pupil. The iris was heavily vascularized, and hyphema was present. The intraocular pressure was RE: 14.6 mm Hg (5.5 g, Schiøtz) and LE: 43.4 mm Hg (10 g, Schiøtz). The left fundus was impossible to visualize. She was treated with acetazolamide (Diamox), bed rest, and binocular eye pads. Two days later the anterior chamber cleared, and an orange mass was seen in the upper half of the fundus. The intraocular pressure was 30 mm Hg. Re-examination one day later, with glycerin to clear the cornea, revealed a round, smooth, solid detachment of the retina with prominent vessels. No fungating mass was seen. The possibility of a malignant tumor in a congenitally defective eye was suspected, and the eye was enucleated on May 22, 1970.

### Microscopic studies

Microscopic examination of the enucleated left eye revealed dilatation of the limbal vessels and perivascular infiltration of neutrophils. A fibrovascular membrane extended between the intact Bowman's membrane and the corneal epithelium, peripherally. The cornea was otherwise not remarkable. Pe-

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology, and The George Washington University Medical Center, Washington, D.C. This study was supported in part by Public Health Service, Grants EY-00032 and EY-00133 from the National Eye Institute. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests to Ramon L. Font, M.D., Ophthalmic Pathology Branch, Armed Forces Institute of Pathology, Washington, D.C. 20305.

*This case was contributed to the Registry of Ophthalmic Pathology by Drs. Hobart A. Lerner and John Abbott of The Genesee Hospital, Rochester, New York, and they have kindly given their permission to report the case.

ripheral anterior synechias occluded the chamber angle. A thin fibrovascular membrane and collections of erythrocytes covered the surface of the iris. Scattered infiltrates of lymphocytes and plasma cells were seen in the iris and ciliary body. Early ectropion uveae was present. The lens was not included in the sections examined. The retina was totally detached, and there were extensive areas of necrosis and infiltration by neutrophils and pigment-laden macrophages, mainly in the outer retinal layers. Several retinal vessels were thrombosed. Blood and proteinaceous exudate filled the subretinal space. Accumulations of lymphocytes and plasma cells were scattered throughout the choroid. Many drusen were seen on Bruch's membrane. A large colobomatous defect involving the optic disk and peripapillary retina was present (Fig. 1). Strands of gliosed retina and islands of proliferated retinal pigment epithelium were present within the sclera at the edges of the colobomatous area (Fig. 2). Large bundles of spindle-shaped cells believed to be smooth muscle extended within the collagenous tissue of the sclera (Fig. 3), reaching between the inner scleral lamellae and the choroid (Fig. 4). These cells, which were arranged in interlacing bundles, showed small round to oval nuclei and abundant acidophilic cytoplasm. The Masson trichrome procedure stained these cells reddish brown, while the phosphotungstic acid-hematoxylin stain revealed numerous dark-blue filaments in their cytoplasm. Cross-sections of the optic nerve demonstrated a complete failure of formation of the meningeal sheaths, severe atrophy of nerve bundles, and astrocytic gliosis. The dysplastic remnants of optic nerve were surrounded by adipose tissue containing strands of smooth muscle and scattered blood vessels (Fig. 5).

*Histopathologic diagnoses*—Our diagnoses were as follows: congenital coloboma of optic disk and peripapillary retina containing large intrascleral bundles of smooth muscle; dysplasia of optic nerve with lipomatosis and failure of formation of leptomeningeal sheaths; rubeosis iridis and periph-

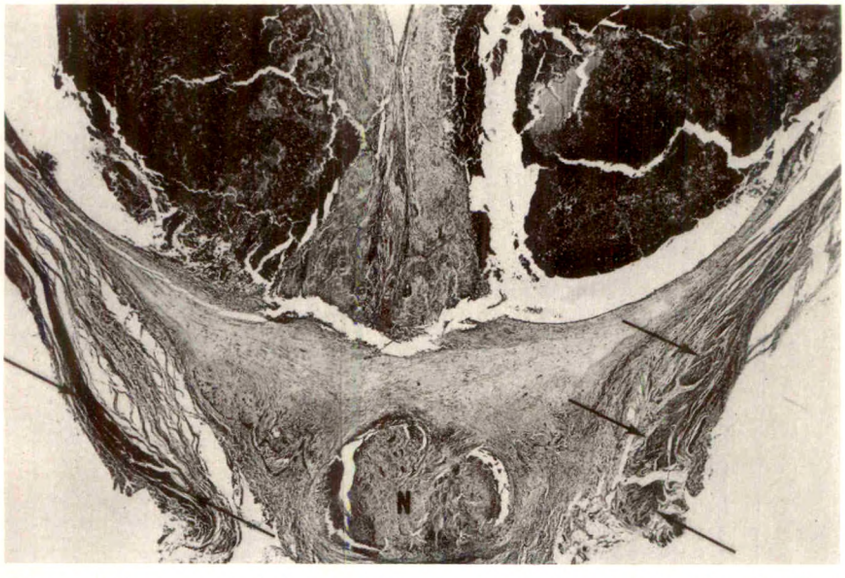



Fig. 1 (Font and Zimmerman). A large colobomatous defect of optic disk and peripapillary retina is present. Fascicles of smooth muscle (arrows) are embedded within the sclera on both sides of the dysplastic optic nerve (N). The retina is totally detached, and blood fills the subretinal space (Masson stain, ×9, AFIP Neg. 70-7276).

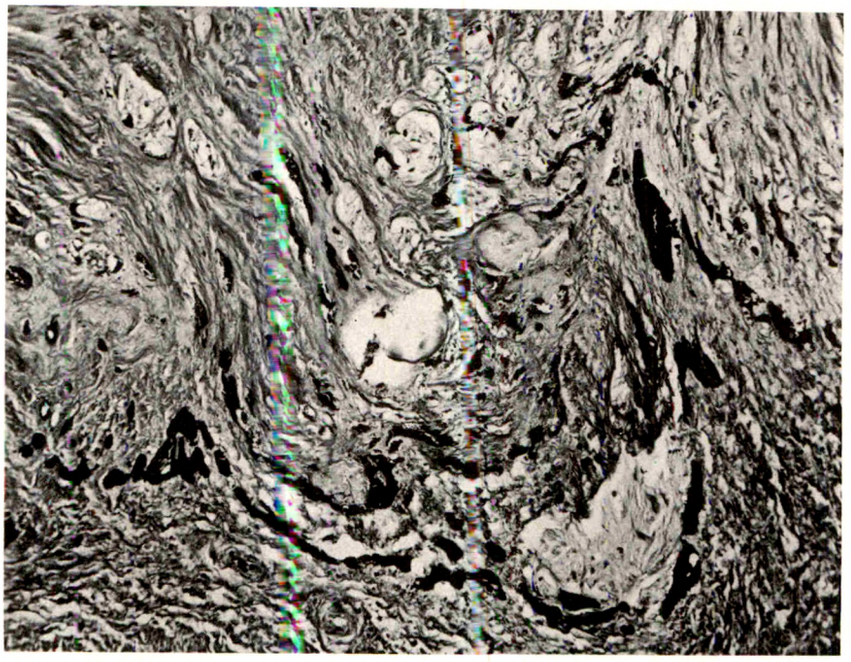


Fig. 2 (Font and Zimmerman). Marked pseudoadenomatous proliferation of the retinal pigment epithelium and strands of glial tissue are seen at the edge of the coloboma (hematoxylin-eosin, ×90, AFIP Neg. 70-7761).

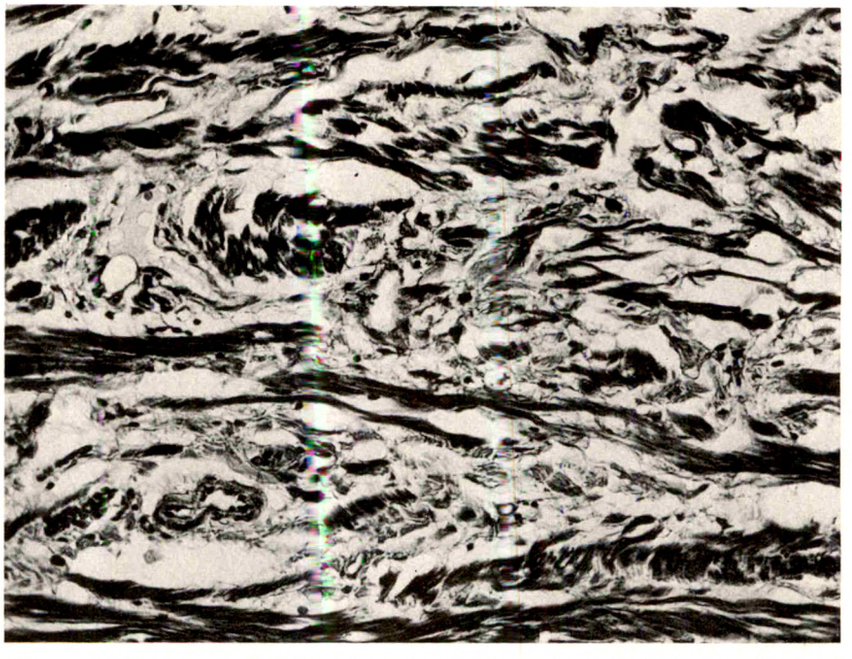


Fig. 3 (Font and Zimmerman). Bundles of smooth muscle are located within the collagenous tissue of the sclera (Masson stain, ×195, AFIP Neg. 70-7281).

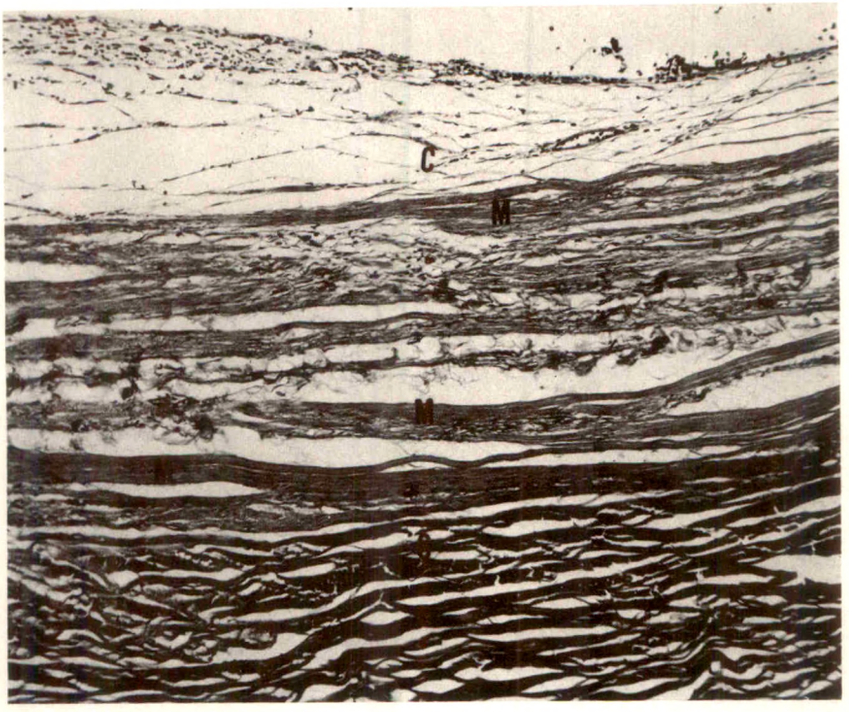



Fig. 4 (Font and Zimmerman). Parallel bundles of smooth muscle (M) are interspersed between the choroid (C) and sclera (S) (hematoxylin-eosin, ×80, AFIP Neg. 70-7283).

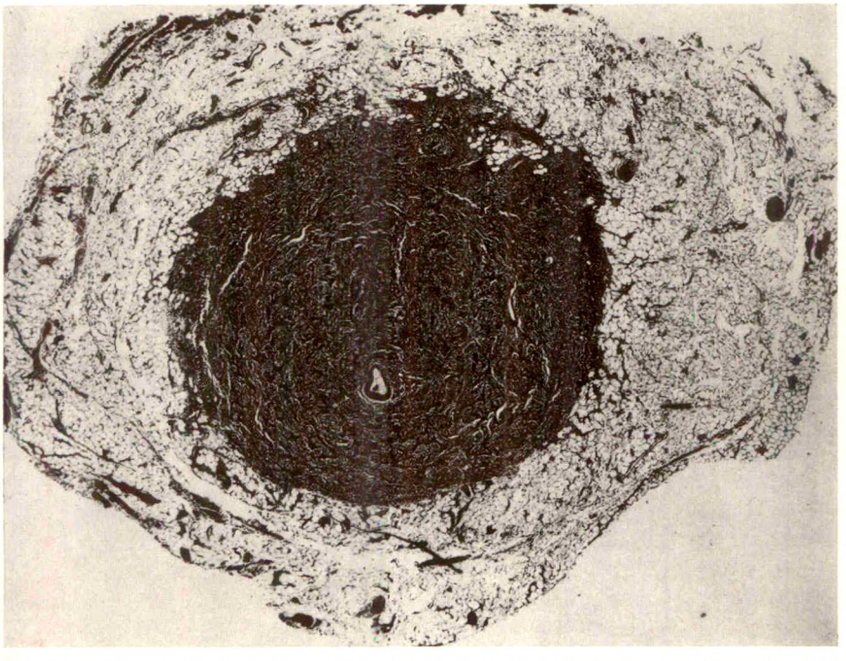


Fig. 5 (Font and Zimmerman). Cross-section of the markedly dysplastic atrophic optic nerve showing lipomatosis and an absence of the meningeal sheaths (Masson stain, ×15, AFIP Neg. 70-7284).

eral anterior synechias; chronic nongranulomatous uveitis; total retinal detachment, with areas of retinal necrosis; large subretinal hemorrhage.

Electron microscopic studies of the formalin-fixed, paraffin-embedded tissue were undertaken, after specially stained sections had been prepared from the re-cut paraffin blocks. The method employed to process the specimen for electron microscopy has been previously described from our laboratory.[1] The sections were stained with uranyl acetate and lead citrate and examined in the RCA model 3G electron microscope. We found remarkably good preservation of cytologic details that permitted us to identify the intrascleral bundles of spindle-shaped cells unequivocally as smooth muscle cells.

All the ultrastructural criteria that are used for identification of smooth muscle cells were satisfied (Figs. 6 and 7).[2] These include: (1) myriad intracytoplasmic filaments, often arranged parallel to the main axis of the cells; (2) scattered oval or fusiform areas of density lying within the masses of intracytoplasmic filaments; (3) similar cytoplasmic densities in continuity with the limiting plasma membranes; (4) almost complete investment of each cell by a basement membrane; and (5) numerous pinocytotic vesicles (or "caveolae") connected to the plasmalemma.

## Summary

The congenitally malformed blind left eye of a 13-year-old girl was enucleated because of the possibility that it contained an intraocular neoplasm. Microscopic examination revealed an unusual colobomatous malformation of the optic disk and nerve. Bundles of smooth muscle were conspicuously present on both sides of the nerve within the sclera

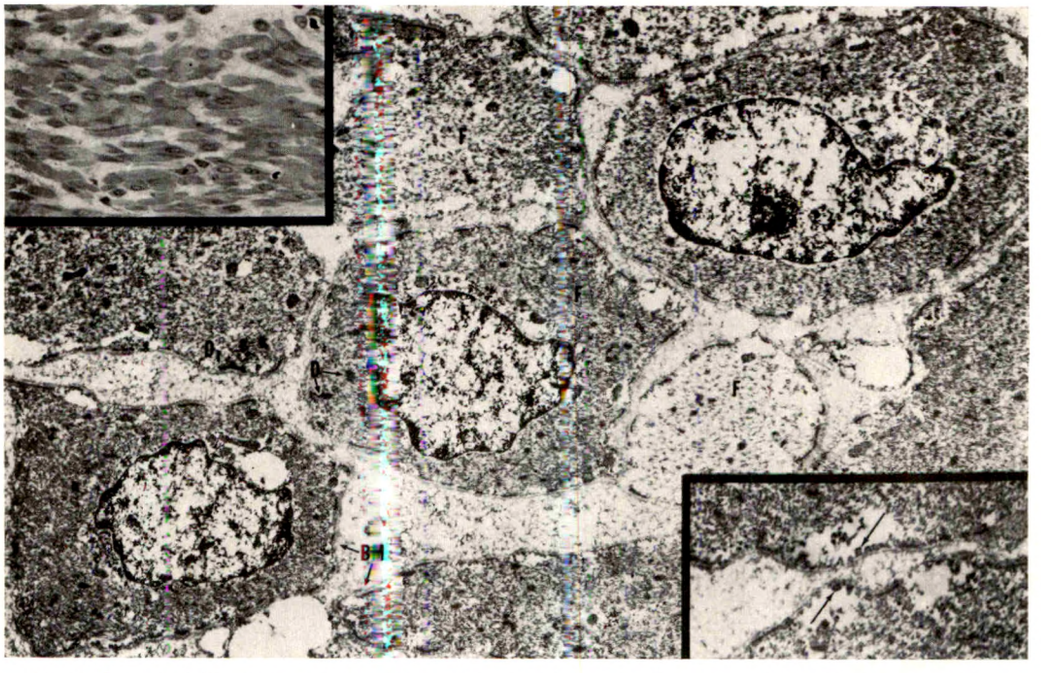



Fig. 6 (Font and Zimmerman). Smooth muscle cells almost totally surrounded by basement membranes (BM) and containing myriad intracytoplasmic filaments (F) with associated dense patches (D), some of which are connected to the plasma membrane ($D_1$) (large micrograph, ×11,000, AFIP Neg. 70-9896-2). The inset in the upper left corner shows the parallel bundles of smooth muscle cells (toluidine blue, ×440, AFIP Neg. 70-7277). The inset in the right lower corner reveals the numerous micropinocytotic vesicles or "caveolae" (arrows) that are attached to the plasmalemma (×21,000).

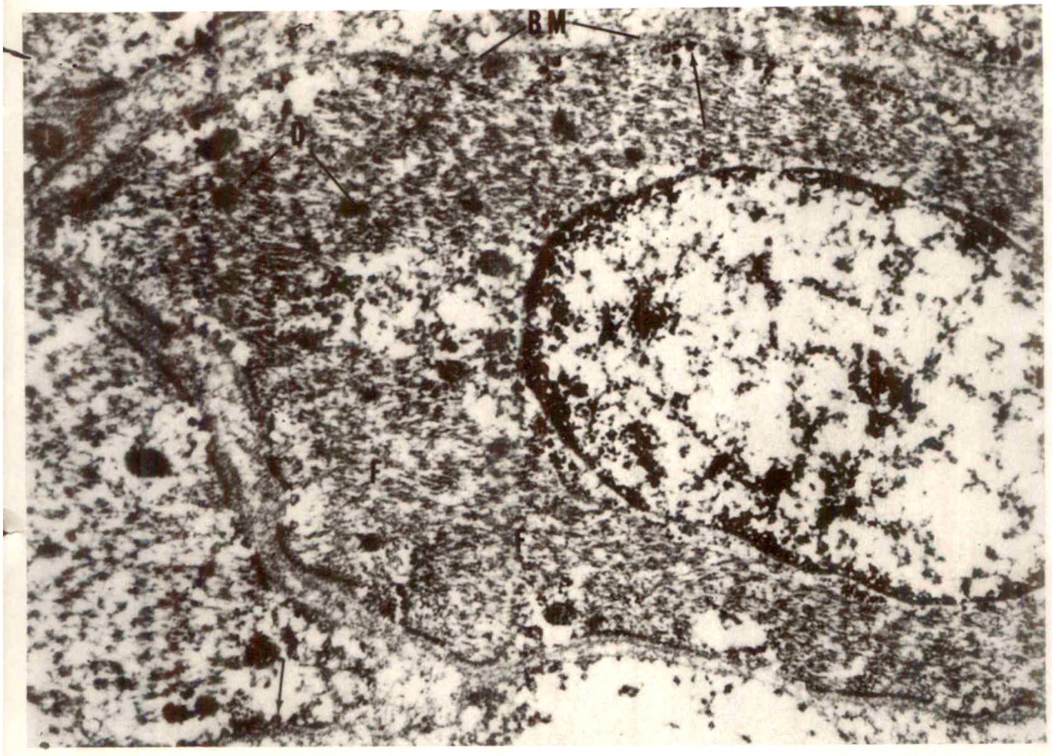



Fig. 7 (Font and Zimmerman). Higher magnification of a smooth muscle cell that is surrounded by basement membrane (BM) and shows intracytoplasmic filaments (F), focal densities (D), and micropinocytotic vesicles or "caveolae" (arrows) (×21,000, AFIP Neg. 70-9896-1).

and between the sclera and choroid. Electron microscopic examination of the formalin-fixed, paraffin-embedded tissue provided unequivocal evidence in support of the interpretation that smooth muscle was present in the sclera.

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# DELAYED SPONTANEOUS HYPHEMA FOLLOWING SUCCESSFUL SCLEROTOMY WITH CAUTERY IN THREE PATIENTS

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Complications after successful external filtering operations for open-angle glaucoma have been extensively catalogued in the ocular literature. Cataracts have been noted in approximately 30 to 40% of such patients.[1-3] Postoperative uveitis is another frequent finding, whereas persistent hypotony is noted much less commonly.[4] Ruptured blebs have been ascribed both to trauma and to infection, or may predispose to the latter.

This paper presents a report of three cases in which hyphema was a late complication of external filtering procedures which, to our knowledge, has not been previously described.

## CASE REPORTS

*Case* 1—A sclerotomy with cautery and peripheral iridectomy was performed on the right eye of a 74-year-old white woman in 1965 because of continued visual field loss despite maximal medical therapy. A similar procedure was performed on the left eye two years later. Thereafter, intraocular pressures and outflow facilities remained well within the normal range in the absence of therapy.

Almost five years after the right eye surgery, the patient was seen complaining of sudden onset of blurred vision on the right with a mild feeling of ocular discomfort and irritation. Examination disclosed the anterior chamber to be approximately half filled with bright red, unclotted blood. An area of subconjunctival hemorrhage was noted superonasal to the filtration site. The remainder of the ocular examination, including intraocular pressure, was within normal limits.

The patient was put to bed with her head elevated to 30°, bilaterally patched, and total resorbtion of the hyphema occurred within 48 hours. She denied any antecedent trauma and was found to be normotensive and without disturbances in her clotting mechanism. Gonioscopy performed immediately after resorbtion of the hyphema disclosed no aberrant vessels in the angle or fistulous tract.

Subsequent follow-up has vevealed no permanent alteration in the patient's aqueous dynamics or in the appearance of the filtration bleb.

*Case* 2—A sclerotomy with cautery and peripheral iridectomy was carried out on the right eye of a 33-year-old white man with advanced juvenile glaucoma in 1963. Two weeks postoperatively, his visual acuity in the operated eye was 20/20 with correction.

Five weeks postoperatively, the patient noted right eye blurring and a miniscule hyphema was seen on examination. This cleared within 24 hours without therapy and the patient remained asymptomatic. Nine months later, the patient had a recurrence of hyphema and, during the ensuing three years, he had at least 20 episodes of intraluminal bleeding. Clearing was always prompt and the patient learned to recognize the hyphema grossly in the pathognomonic manner. At no time were aberrant vessels seen by gonioscopy. At no time did intraocular pressure rise, nor was any abnormality ever noted in the patient's filtering bleb, sclerotomy site, or angle.

No bleeding has occurred for the past two years, the patient's intraocular pressure is 10 mm Hg and his outflow facility is 0.32 $mm^3$ $min.^{-1}$ $Hg^{-1}$ without medications.

*Case* 3—A 58-year-old white woman underwent a left sclerotomy with cautery and peripheral iridectomy for uncontrollable open-angle glaucoma in 1967. Her postoperative course was uneventful and eight weeks after surgery the patient's visual acuity returned to its preoperative level. Two years after the procedure, the patient had blood filling a quarter of the anterior chamber in the operated eye, which cleared within 48 hours without therapy. Four months later, a second, smaller hyphema occurred which also cleared spontaneously. No alteration in the patient's glaucoma control resulted and, at present, her intraocular pressure is 16 mm Hg and her outflow facility 0.20 $mm^3$ $min.^{-1}$ $Hg^{-1}$. In each instance, gonioscopy failed to disclose any source for the recurrent hemorrhage.

## DISCUSSION

Three patients with spontaneous hyphema occurring or recurring more than two years after successful external filtration procedures are presented. In no case was there an antecedent history or the physical findings of trauma, infection, hypertension, or abnormal clotting mechanisms. In each instance, the

From the Department of Ophthalmology of the New York Medical College. This study was supported in part by Public Health Service Grant NB-07162-04, Grant 69-869 from the American Heart Association, and by Grant T-517 from the American Cancer Society, Inc.

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presenting complaints were of the sudden onset of decreased visual acuity. Usually, this was associated with some ocular irritation, but pronounced pain and discomfort were not noted.

Two of the three patients had repeated episodes of hyphema, and only one required therapy with bilateral, occlusive eye patches and bed rest. In all instances, prompt resorbtion of blood from the anterior chamber occurred. Elevation in the intraocular pressure did not occur at any time when blood was present in the anterior chamber, nor did it interfere in any way with the long-term success of the surgical result.

The collagenolytic effect of aqueous has been used to explain the progressive polycystic nature of bleb formation.[5] Small vessels which might bridge a scleral area that is progressively "digested" might rupture as support is lost. It is, however, interesting to note that most successful blebs are ischemic and that aqueous appears to retard episcleral blood vessel growth.[5] The exact mechanism of the hyphema phenomenon, however, remains obscure.

## Summary

Vision became blurred in a 74-year-old woman with open-angle glaucoma five years following sclerotomy with cautery and peripheral iridectomy. The anterior chamber was one-half filled with bright red, clotted blood and a subconjunctival hemorrhage was noted above and nasal to the filtration site. No cause was found and the blood resorbed in 48 hours with bed rest. Sclerotomy and cautery with peripheral iridectomy in a 33-year-old white man was followed five weeks later by a minute hyphema and blurring of vision. Bleeding recurred at least 20 times in the subsequent three years, but there was none in the subsequent two years. A 58-year-old white woman with similar surgery had hyphema on two occasions during the four months following surgery.

In all three patients, the hyphema cleared spontaneously, did not impair aqueous humor dynamics, and was not associated with visible blood vessels in the angle examined by gonioscopy.

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# CHOLINESTERASE ISOENZYMES IN HUMAN OCULAR TISSUE HOMOGENATES

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The enzyme cholinesterase has been described in animal and human ocular tissues.[1-3] Its function, other than its role in autonomic nervous system, has not been clarified. Rabbit plasma contains principally true cholinesterase.[4] The rabbit eye has mostly true cholinesterase isoenzymes in the sclera, cornea, iris, ciliary body, lens capsule, retina-choroid, optic nerve, aqueous and vitreous humors.[5] Pseudocholinesterase was found in small amounts in these tissues except in the aqueous, vitreous, and lens capsule.[5] The cholinesterase in normal human plasma was shown to consist of pseudocholinesterase isoenzymes.[6] It seemed important to determine the nature of the cholinesterase isoenzymes in human ocular tissues.

## Materials

Eighty fresh human eyes, obtained from the eye bank, were partitioned into sclera, cornea, iris, ciliary body, retina, choroid, optic nerve, and vitreous. Aqueous and lens capsules were obtained from patients undergoing cataract surgery. The tissues were homogenized (10-20% w/v) in 0.1 M phosphate buffer, pH 8.0. The homogenates were centrifuged at 13,000 × g for 20 minutes in a refrigerated centrifuge. The supernatants were divided into aliquots, quick frozen, and stored at −20° C until used.

## Methods

Disk electrophoretic separation of the proteins in the ocular tissue homogenates was performed according to the technique of Ornstein[7] and Davis[8] in glass tubes, 10 cm long and 0.5 cm internal diameter, containing 1.4 ml of separation gel, and 0.4 ml spacer gel. Protein determinations in the homogenates was performed according to Lowry,[9] using lyophilized crystallized bovine serum albumen (BSA), as a standard.

In each determination, we used sets of four identical columns—i.e., the gels were prepared at the same time, layered with equal amounts of a particular homogenate, and resolved in the same operation. One column was incubated with AcSCh, as substrate. The second column was incubated with AcSCh and $10^{-4}$M BW. The third contained AcSCh and $5 \times 10^{-5}$M iso-OMPA. The fourth had BuSCh as substrate. In addition, a set of 10 columns each containing a specific tissue homogenate was incubated using AcSCh as substrate and $10^{-5}$M eserine.

The cholinesterase isoenzyme analysis is based on the thiocholine method of Koelle and Friedenwald,[10] by which the thiocholine formed from the AcSCh or BuSCh hydrolysis is precipitated as copper thiocholine and appears as a white band at the enzyme site on the gel column. The copper thiocholine is subsequently stained with dithioxamide. The method for the preparation of the gels and

### Chemicals and abbreviations

AcSCh = acetylthiocholine iodide
PrSCh = propionylthiocholine iodide
BuSCh = butyrylthiocholine iodide
AChE = true or acetylcholinesterase
BSA = bovine serum albumin
nsChE = pseudo or nonspecific cholinesterase
ChE = cholinesterase
eserine = physostigmine sulfate
iso-OMPA = tetra-isoprophylphrophosphoramide
1:5 bis-4-allyldimethxlammomiumphenyl
BW = pentam-3-one dibromide 284 C51

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buffers and the procedure for the staining of the bands has been fully described by Juul.[6]

## Results

The columns incubated with AcSCh as substrate and $10^{-5}$M eserine showed no enzyme activity, that is no bands formed on the gel columns. The columns incubated with AcSCh only, gave varying numbers of bands depending on tissue used. The columns incubated withBuSCh as substrate failed to develop any bands. The columns incubated with AcSCh plus $5 \times 10^{-5}$M iso-OMPA were completely identical with the columns incubated with AcSCh only. The columns incubated with AcSCh plus $10^{-4}$BW showed complete inhibition of enzyme activity—i.e., no bands appeared. The results are summarized in Table 1.

TABLE 1

NUMBER OF BANDS OBTAINED BY INCUBATION WITH SUBSTRATE (AcSCh) AND SUBSTRATE PLUS INHIBITORS USING DISK ELECTROPHORESIS

| Tissue | Substrate Alone | Substrate Plus BW $10^{-4}$ or $10^{-5}$ Eserine | Substrate Plus iso-OMPA $10^{-5}$ |
|---|---|---|---|
| Sclera | 2 | 0 | 2 |
| Cornea | 1 | 0 | 1 |
| Iris | 3 | 0 | 3 |
| Ciliary body | 5 | 0 | 5 |
| Aqueous | 1 | 0 | 1 |
| Lens capsule | 1 | 0 | 1 |
| Retina | 3 | 0 | 3 |
| Choroid | 4 | 0 | 4 |
| Vitreous | 1 | 0 | 1 |
| Optic nerve | 2 | 0 | 2 |

## Discussion

A characteristic of cholinesterases is their pronounced sensitivity to low concentrations of eserine, and this fact may be used to distinguish cholinesterases from other tissue esterases.[11] It has been shown that a $10^{-5}$M concentration of eserine causes complete inhibition of cholinesterases while being without effect on other tissue esterases.[12] In our experiments, when the preincubation and incubation mixtures contained $10^{-5}$M eserine, a complete inhibition of AcSCh hydrolysis was effected; that is, no bands appeared on the gel column. This indicates that, under the conditions of the experiment, only cholinesterases are being analyzed. Of the three widely used methods, namely, substrate inhibition, substrate specificity, and selective inhibition, to distinguish between the cholinesterases, the latter two methods are suitable for disk electrophoresis.

*Substrate specificity*—True cholinesterase (AChE) hydrolyses AcSCh more rapidly than PrSCh and PrSCh more rapidly than BuSCh. Pseudocholinesterase (ns-ChE), on the other hand, hydrolyses PrSCh or BuSCh more rapidly than AcSCh[13]. In our experiment, the gel columns incubated with BuSCh as substrate did not show any bands (Figs. 1 and 2).

*Selective inhibition*—Certain inhibitors, at a given concentration, selectively inhibit one type of cholinesterase while having practically no effect on the other type. It has been shown that $10^{-6}$M iso-OMPA inhibits selectively ns-ChE while $10^{-5}$M BW inhibits AChE only.[14] For the method used, it was found that a concentration of $5 \times 10^{-5}$M iso-OMPA and $10^{-4}$M BW was best suited for differentiation between true and pseudocholinesterase.[5]

In our experiment, $10^{-4}$M BW completely inhibited the enzyme activity, while $5 \times 10^{-5}$M iso-OMPA had no inhibiting effect at all. The results of these experiments indicate the human ocular tissue enzyme to be true cholinesterase. Purified enzymes (Sigma Chemical Company), used in amounts to give the same total activity as in the ocular tissues, when taken through the same regimen gave similar results; that is, the purified enzymes were selectively inhibited by the inhibitors used in the given concentrations. Also, the purified true cholinesterase did not hydrolyse BuSCh—i.e., no bands were obtained.

Disk electrophoretic separation of the isoenzymes was used because of its superiority

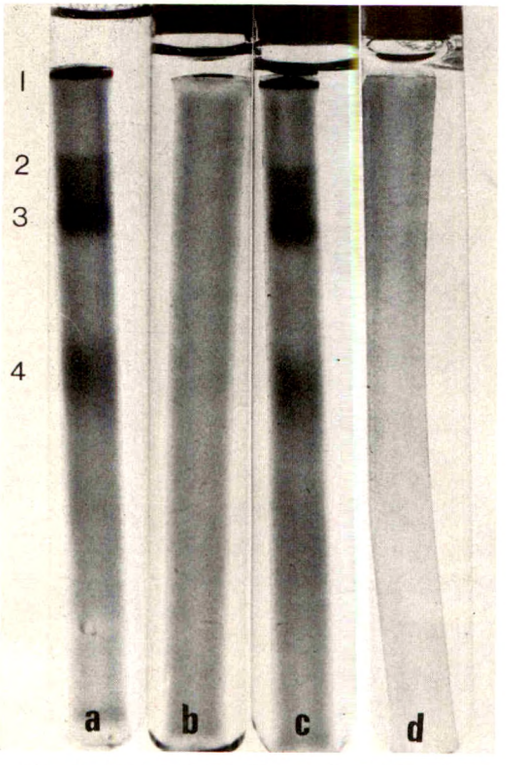



Fig. 1 (Leopold and Furman). Cholinesterase isoenzymes in human choroid. (a) With acetylthiocholine as substrate, four bands can be identified: 1 = thin, intense band, 2 = wide, diffused band, 3 = medium, intense band, and 4 = wide, diffused band. (b) With acetylthiocholine plus BW $10^{-4}$M, there is inhibition of all activity; column is completely clear. (c) With acetylthiocholine plus iso-OMPA $5 \times 10^{-5}$M, there is no inhibition of acidity. Bands are the same as in (a). In (d), with butyrylthiocholine as substrate, there is no activity.

over other electrophoretic methods. Juul[6] for example, was able to demonstrate twelve ChE isoenzymes in human plasma by disk electrophoresis, as compared to seven isoenzymes obtained by other investigators.[15] Additionally, this method appeared best suited for the experiment. The separation of ChE-isoenzymes proved to be extremely difficult. This may be due to their similar molecular properties and to the unequal distribution of activity between the individual bands. To effect a meaningful separation, the amount of acrylamide in the separation gel, the time allowed for electrophoresis, the time allowed for the development of the bands, the quantity of protein used per column had to be determined empirically. The data are presented in Table 2. Because of the restrictive nature of this study the results may be in variance with results obtained by other investigators using other techniques.[3]

## Summary

Proteins of human ocular tissue homogenates were separated by disk electrophoresis. By the use of specific substrates and selective inhibitors, it is shown that only true cholinesterase is present in the ocular tissues

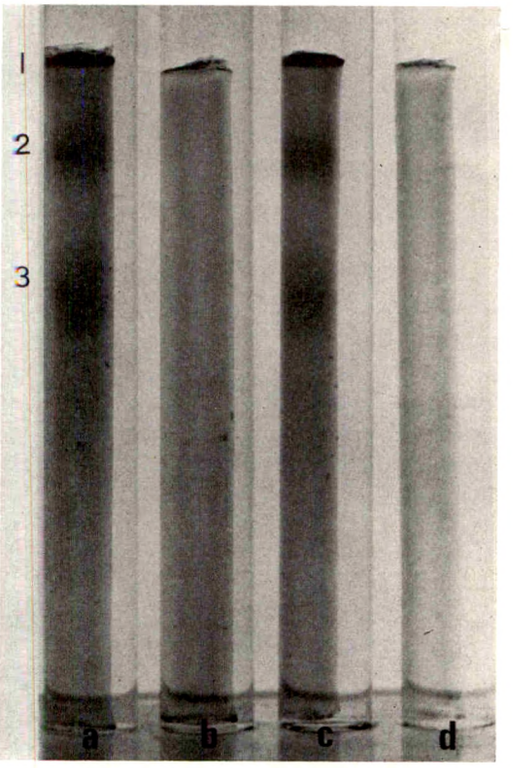



Fig. 2 (Leopold and Furman). Cholinesterase isoenzymes in human iris. (a) With acetylthiocholine as substrate, three bands can be identified: 1 = thin, intense band, 2 = medium, diffused band, 3 = wide, diffused band. (b) With acetylthiocholine plus BW $10^{-4}$M, there is complete inhibition of activity. (c) With acetylthiocholine plus iso-OMPA $5 \times 10^{-5}$M, there is no inhibition of activity, as in column (a). (d) With butyrylthiocholine as substrate, there is no activity.

TABLE 2

CONDITIONS FOR SEPARATION OF ISOENZYMES*

| Tissue | Acrylamide in Separation Gel (in %) | Amount of Protein per Column (in μg) | Time for Electro-phoresis (in hours) | Incubation Time |
|---|---|---|---|---|
| Sclera | 9.5 | 200 | 7 | Overnight at 4° C |
| Cornea | 9.5 | 200 | 7 | Overnight at 4° C |
| Iris | 8.0 | 100 | 6 | Six hours at room temperature |
| Ciliary body | 8.0 | 120 | 6 | Six hours at room temperature |
| Aqueous | 7.5 | 150 | 7 | Seven hours at room temperature |
| Lens capsule | 7.5 | 200 | 7 | Overnight at 4° C |
| Retina | 7.5 | 200 | 8 | Overnight at 4° C |
| Choroid | 8.0 | 100 | 8 | Five hours at room temperature |
| Vitreous | 7.5 | 180 | 7 | Overnight at 4° C |
| Optic nerve | 8.0 | 150 | 6 | Six hours at room temperature |

* Empirically determined.

analyzed. The number of isoenzymes (bands) varies with a given tissue.

ACKNOWLEDGMENTS

We thank Doctor Castroviejo and The Manhattan Eye Bank for additional specimens used in this study.

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# LINCOMYCIN LEVELS IN RABBIT OCULAR FLUIDS AND SERUM

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Lincomycin hydrochloride monohydrate is derived from the actinomycete, Streptomyces lincolensis, var. lincolnensis (Mason, Dietz, and DeBoer[1]). The mechanism of its antibacterial activity is probably through inhibition of bacterial protein synthesis. The antibiotic is active in vitro primarily against Gram-positive coccal microorganisms with the exception of the enterococci. Kohn, Hewitt, and Fraser,[2] as well as Saunders, Foster, and Scott,[3] report that lincomycin-resistant strains of Group A streptococci have been isolated in some patients undergoing treatment with this antibiotic.

Lincomycin does penetrate the blood–brain barrier, producing significant detectable cerebrospinal levels in the presence of inflamed meninges, according to Kaplan, Chew, and Weinstein.[4] These authors also report that, in the presence of meningeal infection, the level of the drug in the cerebrospinal fluid is about 40% of that in the blood. Becker[5] reports that in 14 patients given lincomycin before routine eye surgery, significant levels were observed in all samples except one taken from a patient in whom the drug had been administered orally. The other 13 patients were given the drug parenterally; 11 received 2.4 g intramuscularly in multiple doses, and two patients received the drug intravenously, all in the same dosage. Following the last injection in patients with noninflamed eyes, the average lincomycin level of the aqueous humor was 1.3 μg/ml after one and one-half to two hours. After intramuscular injection, the aqueous humor level in the affected eye (glaucoma, staphyloma) was 21 μg/ml, and in the same time period the serum levels ranged from 10.2 to 23 μg/ml. Boyle, Lichtig, and Leopold[6] report that significant concentrations appeared in the aqueous humor as early as two minutes after lincomycin was injected subconjunctivally (0.25 ml of a solution containing 300 mg/ml) in 20 patients with noninflamed eyes who were hospitalized for elective ocular surgery (usually cataract extraction). Peak levels of the antibiotic in the aqueous humor occurred between one and three hours, while minimal levels persist in the serum and aqueous humor for 12 hours after injection.

In the study reported here, we measured the concentration of lincomycin in the aqueous humor, vitreous humor, and serum of normal rabbits after administration by various routes—intramuscular, intravenous, and subconjunctival—and the results were compared.

## MATERIALS AND METHODS

All rabbits used in this study weigh 1.5 to 4.0 kg. The average dose per animal was 15 to 20 mg/kg. Lincomycin HCl monohydrate, 300 mg/ml, was diluted to 50 mg/ml with sterile sodium chloride and then administered intramuscularly or intravenously; another series of rabbits received 0.1 ml of a 300 mg/ml solution of lincomycin subconjunctivally to each eye. Samples of aqueous humor, vitreous humor, and serum were obtained at one-half, two-, four-, and six-hour intervals, following the intramuscular and intravenous administrations, and one- and four-hour intervals after subconjunctival injection.

The ocular fluids and serum were assayed for lincomycin by the tube dilution method.

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This method consists of an arithmetic progression of aliquots of standard antibiotic with the addition of media in inverse amounts to achieve a constant total volume of 1.0 ml per tube in all tubes.

The inoculum of the test organism, Sarcina lutea (FDA No. 1001), was prepared by inoculating glucose broth from a stock agar slant maintained at 4 to 6°C. After incubation at room temperature for 24 hours, extent of growth was determined and adjusted on a Lumetron colorimeter with a number 650 mμ filter until an optical density reading of 0.15 was obtained. This suspension was then diluted $10^{-3}$. Fresh 1.5% trypticase soy broth, pH 7.0, was employed as the medium and diluent.

The minimum inhibitory concentration of the lincomycin standard was determined. The standardized Sarcina lutea test inoculum was found to be consistently inhibited by 0.15 μg/ml of the lincomycin standard solution.

The volume of test sample and volume of standard inoculum employed in all assays was 0.5 ml of each per tube to obtain a total volume in each tube of 1.0 ml. Appropriate controls were also prepared to verify the sterility of samples and medium, and also the viability of the test organism. The minimum concentration of lincomycin that could be detected by this procedure was 0.3 μg/ml.

## Results

The levels of lincomycin in the aqueous humor, vitreous humor, and serum of normal rabbits following intramuscular, intravenous and subconjunctival administration are indicated in Table 1.

*Intramuscular administration*—Lincomycin was present in detectable concentration in the aqueous humor of all of the test rabbits but was not detectable in the vitreous humor of most of the animals. At one-half hour the highest concentration in the aqueous humor was 1.0 μg/ml and in the serum 10.3 μg/ml. Aqueous humor levels tapered off gradually with no marked decline up to six hours. As opposed to this situation, the serum levels declined rapidly between one-half and two hours; between two and six hours the decline was more gradual.

*Intravenous administration*—Lincomycin was detected in the aqueous humor, serum, and in the vitreous humor only after the one-half and the two-hour aspiration. At one-half hour, the highest concentration found in the aqueous humor was 1.19 μg/ml and in serum 6.44 μg/ml. Decline in the aqueous humor and serum levels followed the same

TABLE 1

LINCOMYCIN LEVELS IN THE SERUM, AQUEOUS HUMOR, AND VITREOUS HUMOR OF NORMAL RABBITS AT VARYING INTERVALS AFTER INTRAMUSCULAR (IM), INTRAVENOUS (IV), AND SUBCONJUNCTIVAL (SC) INJECTIONS

| Time (in hours) | Route of Administration | Serum Levels (μg/ml) | | Aqueous Levels (μg/ml) | | Vitreous Levels (μg/ml) | |
|---|---|---|---|---|---|---|---|
| | | Average | Range | Average | Range | Average | Range |
| 1/2 | IM | 10.3(10)* | 3.2 –15 | 1.0(7) | 0.75–1.5 | | |
| | IV | 6.44(7) | 3.3 –15 | 1.19(9) | 0.75–1.5 | 0.39(3) | 0.33–0.5 |
| 1 | SC | Not detectable | | >15(2) | | | |
| 2 | IM | 4.16(13) | 2.25–7.5 | 0.92(9) | 0.5 –1.5 | | |
| | IV | 1.96(7) | 0.5 –3 | 0.87(5) | 0.6 –1.5 | 0.47(4) | 0.37–0.5 |
| | IM | 1.78(8) | 0.75–2.25 | 0.75(5) | 0.5 –1.25 | | |
| 4 | IV | 1.25(6) | 0.5 –2.25 | 0.83(3) | 0.5 –1.0 | | |
| | SC | Not detectable | | >0.75(2) | | | |
| 6 | IM | 1.64(8) | 0.5 –2.25 | 0.64(6) | 0.5 –0.83 | | |
| | IV | 0.62(11) | 0.37–0.75 | 0.44(2) | 0.37–0.5 | | |

* Figure in parenthesis represents the number of rabbits in each group.

pattern of decline observed after intramuscular injection. The aqueous level tapered off gradually, whereas the serum level rapidly declined between one-half and two hours, and then tapered down slowly between two and six hours. The concentration of lincomycin in the vitreous humor was slightly greater at two hours than at one-half hour, but the antibiotic could not be detected at the four- and six-hour assays.

*Subconjunctival administration*—Lincomycin penetrated the aqueous humor of the test rabbits, but no perceptible level of lincomycin was found in the serum or vitreous humor. The aqueous humor lincomycin concentration after subconjunctival injection exceeded 15 μg/ml after one hour but at four hours the level was found to be greater than 0.75 μg/ml.

## Comment

The design of the assay was planned to accommodate the small volume of each sample that could be aspirated from the eye of a rabbit—approximately 0.2 ml of aqueous humor and 0.75 ml vitreous humor. It was necessary to pool the aqueous from both eyes of each animal, at each time interval, in order to have enough sample to perform the assay. The vitreous humor from each eye was assayed individually.

Comparison of the serum levels, following intramuscular and intravenous administration, revealed similar curves. The serum levels after intramuscular administration were found to be higher than the serum levels after intravenous administration at all time intervals tested. It is possible that the intravenous concentration peaked prior to the 30-minute specimen. Kaplan and associates[4] reported finding no significant differences in serum levels in humans when intramuscular and intravenous injections are compared. The aqueous humor level after intravenous administration was found to be somewhat higher than after intramuscular injection at one-half hour but, after one and one-half hours, it was slightly lower than the intramuscular injection. With both intramuscular and intravenous injections a gradual straight line decline was noted. Lincomycin did penetrate the vitreous humor after intravenous administration up to at least two hours, but beyond two hours no lincomycin could be detected by the assay method employed. Subconjunctival administration produced the highest intraocular concentrations obtained in this study. Kaplan and associates[4] showed that concentrations of lincomycin required to inhibit 60 strains of Staphylococcus aureus ranged from 6.2 to 0.75 μg/ml, against eight strains of Streptococcus pyogenes from 1.5 to 0.09 μg/ml, against six strains of Streptococcus viridans from 0.75 to 0.19 μg/ml, and against five strains of Diplococcus pneumoniae from 1.5 to 0.19 μg/ml.

It is evident that the required antibacterial concentration for the above bacteria is readily achievable in the serum after both intramuscular and intravenous injection after one-half hour, and for some strains up to six hours (Fig. 1). Concentration of lincomycin obtained in the aqueous humor is adequate

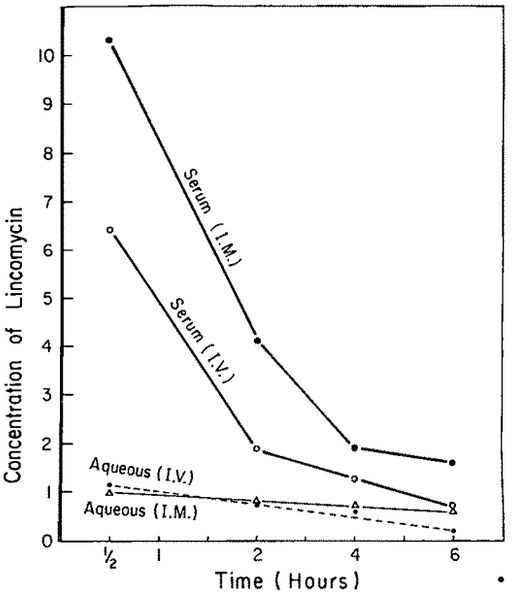



Fig. 1 (Coles, Boyle, Leopold, and Schneierson). Average lincomycin levels (in μg/ml) in aqueous humor and serum at varying time intervals following intramuscular and intravenous injections.

against all strains with a minimal inhibitory concentration below 1.19 μg/ml after intravenous and 1.0 μg/ml after intramuscular injection at one-half hour. Some but not all of the above bacterial strains will be inhibited by the aqueous humor concentrations. Intravenous injection of lincomycin will achieve antibacterial concentration in the vitreous at one-half and two hours against some strains of Streptococcus pyogenes, viridans streptococci, and Diplococcus pneumoniae.

The concentration of lincomycin in the aqueous humor one hour following subconjunctival administration is theoretically adequate to inhibit all strains with minimal inhibitory concentrations below 15 μg/ml, and most strains will still be inhibited by the concentrations observed up to four hours after administration.

## Summary

A series of experiments were performed to determine the level of lincomycin in the aqueous and vitreous humor of noninflamed eyes and in the serum of rabbits at varying periods following intramuscular, intravenous, or subconjunctival injection. Detectable levels were achieved by all routes of administration within one-half hour and up to six hours after injection. The concentrations found in the serum and aqueous humor were sufficient to be effective against a number of Gram-positive coccal pathogens. Absorption into the vitreous humor was irregular and was of questionable significance in the noninflamed eye.

## Acknowledgment

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# PRILOCAINE AS A LOCAL ANESTHETIC USEFUL IN OPHTHALMIC SURGERY

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Prilocaine (Citanest), an anesthetic agent structurally very similar to lidocaine (Xylocaine), provides excellent local anesthesia for ophthalmic surgical procedures. Since the initial synthesis of prilocaine in 1960, many detailed clinical and laboratory studies have been performed with an emphasis on comparison with lidocaine, considered to be the standard of local anesthetics on the basis of popular ussage. The latency of onset of anesthesia is the same or only slightly longer. The specificity of the anesthesia is the same,[1] the toxicity is 50% that of lidocaine,[1-5] the diffusion of the agent is greater,[5,6] and only minimal irritation is noted locally[1] (Table 1). A cross allergenicity exists with local anesthetics of the amide type such as lidocaine. One of us (LTM) has been using prilocaine routinely as the anesthetic agent for retrobulbar and seventh-nerve infiltrate blocks in private practice. The adequacy and advantages of this agent are reported here.

## METHODS AND RESULTS

A total of 508 surgical cases were performed in a private hospital utilizing prilocaine without epinephrine as the sole anesthetic agent (Table 2). All surgery was performed at an altitude of 5280 feet (Denver, Colorado), with a large number of patients not acclimated to this high altitude. A cardiac monitor was attached in all cases except photocoagulations and non-surgical cryocoagulations. Approximately 3 to 5 ml of 2% prilocaine without epinephrine was used for the retrobulbar anesthesia and 10 ml for the seventh nerve akinesia. Hyaluronidase (Wydase) was mixed with prilocaine for the cataract procedures. This agent has been used also on patients judged not suitable candidates for general anesthesia, including those with borderline compensated heart failure, hypertensive cardiovascular disease, previous coronary occlusions, heart blocks, and pulmonary emphysema. Fifty-one primary retinal detachment cases were successfully treated, with the shortest case lasting 33 minutes and the longest case lasting two hours and 22 minutes (average duration, one hour and two minutes). Fifty-two intracapsular lens extractions were performed, with the shortest case lasting 25 minutes and the longest one hour and 37 minutes (average duration, 51 minutes). Twenty-nine cases of lens aspiration, external filtration, and peripheral iridectomy were performed, with the shortest case taking five minutes and the longest one hour and 13 minutes. (average duration, 37 minutes). The duration of surgical anesthesia persisting after the procedures were completed was not determined. In addition, 376 photocoagulation and surgical and non-surgical cryocoagulation procedures were performed utilizing the above anesthetic routine. Surgically adequate block was obtained in each case, but three cases complained of some discomfort during the procedure. Repetition of anesthetic block to extend the duration of anesthesia was not necessary. No complications due to central nervous system stimulation or seizures, cardiovascular decompensation, respiratory insufficiency, or cyanosis were noted.

TABLE 1

ADVANTAGES OF PRILOCAINE OVER LIDOCAINE

1. Duration of anesthesia is greater
2. Epinephrine not needed
3. Tissue diffusion greater, systemic adsorption slower
4. Toxicity is 50% less
5. Less local irritation

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## Discussion

Prilocaine is a derivative of aniline and is chemically closely related to lidocaine, phenacetin, acetanilide, and sulfonamide. Prilocaine is marketed as a 1 or 2% solution of 2-propylamino-O-propionotolulidide HCl with sufficient sodium chloride to render the solution isotonic and the pH 6 to 7. Methylpareben is added in multiple-dose vials. Stability in both prilocaine and lidocaine is of indefinite duration. Prilocaine differs in chemical structure from lidocaine mainly by a substitution in the end radical of the side chain (Fig. 1).

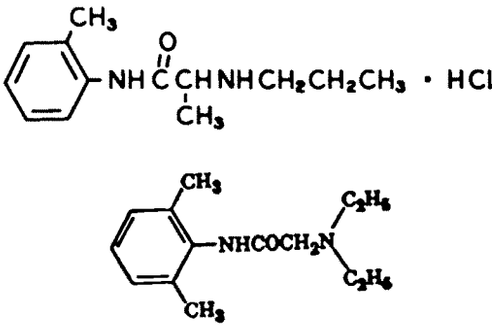



Fig. 1 (Moorman and Kenny). Chemical structure of prilocaine (top) and lidocaine (bottom).

Prilocaine without epinephrine has been used successfully for a variety of ophthalmic surgical procedures. The anesthetic has been adequate for primary retinal detachment circling band and buckling procedures, intracapsular lens extraction, anterior segment procedures, and photocoagulations and cryocoagulations.

Of greatest interest to the opthalmologist is the extended duration of anesthesia obtained with prilocaine. Various authors[6-8] have demonstrated that the duration of anesthesis produced by 2% prilocaine is of 25% longer duration than that produced by lidocaine. This 30-minute extension of anesthesia (from 115 to 146 minutes) is highly significant. It enables the performance of complicated ophthalmic procedures without the addition of epinephrine to the agent. Sudove[5] has noted that regional blocks with 2% prilocaine will last approximately two hours and 40 minutes without epinephrine. We have found that such duration of anesthesia is adequate for the performance of extended retinal detachment procedures in clinical practice. The increased duration of anesthesia seems to be related to a 50% decrease in vasodilating effect as compared with lidocaine.[2]

TABLE 2

PRILOCAINE IN OPHTHALMIC SURGERY

| Procedure | No. Cases |
|---|---|
| Retinal detachment | 51 |
| Anterior segment procedures | 29 |
| Intracapsular lens extractions | 52 |
| Photocoagulations and cryocoagulations | 376 |
| Total | 508 |

A greater margin of safety is evidenced with prilocaine, as it has a toxicity factor which is only 50% that of lidocaine.[1,2,5,9,10] Toxicity effects noted with lidocaine range from mild drowsiness, tinnitus, vertigo, apprehension and muscle twitching, to convulsions and coma, respiratory depression, and bradycardia.[11-13] Cardiac depression due to involvement of the heart conduction system has been reported with lidocaine,[11,12] but no such effects have been reported with prilocaine. In separate studies by Astrom and Person,[2] Englesson, Paymaster, and Hill,[3] and Eriksson,[4] it has been demonstrated that prilocaine's toxic effects on the central nervous system are approximately half that of lidocaine using comparable volumes and concentrations of both drugs. A lower central nervous system and cardiovascular effect was noted by Englesson[14] with a 400 mg dosage of prilocaine as compared with a 200 mg dosage of lidocaine. Astrom and Person[2] attributed the lower toxicity of prilocaine to its lower plasma levels which are a result of the decreased vasodilation and absorption rate from the injected area and a higher rate of renal excretion. Englesson, Paymaster, and Hill[3] demonstrated the same seizure pattern in electroencephalograms (EEGs) in dogs,

but twice the dosage was necessary with prilocaine to elicit the same effect as with lidocaine. Eriksson[4] found essentially the same results in experiments using EEGs with simultaneous automatic frequency analysis. This effect seemed to be mediated by a lower blood level and a lower lipid solubility of prilocaine which decreased the degree of brain penetration from the vascular system. In consideration of the decreased central nervous system excitation pattern, prilocaine may be significantly safer in patients with epilepsy.

### Complications and contraindications

A complication reported with prilocaine which does not occur with lidocaine is the production of methemoglobin. Methemoglobin is a form of hemoglobin in which the iron of the heme complex has been oxidized to the ferric form by electron transfer to oxygen. It cannot be disassociated by changes in the oxygen tension. Normally, methemoglobin is continually being formed in the body, is reduced by enzyme reductase, and has a blood concentration rarely exceeding 1% in the normal patient. A rise of methemoglobin in a patient to 5 or 6% of the circulating hemoglobin (0.8 to 1 g%) produces clinical cyanosis. Prilocaine causes the formation of methemoglobin through a breakdown metabolite either of the aromatic chain or the side chain. Clinical studies by Lund[15] showed that with a maximum dose of 600 mg (30 ml of a 2% solution), an average methemoglobinemia of 0.1 g% was found, with a maximum of 0.9 g% occurring in only one person out of the 74 examined. Even with a dosage level of 900 mg and a maximum level of 2.7 g% methemoglobin, no symptoms of hypoxia were noted. Clinically, with doses of 400 mg or less, Lund was unable to note clinical signs of methemoglobinemia. At a 600 mg dosage, some patients developed signs of cyanosis in the nail beds and lips, but no symptoms of cardiovascular or central nervous system involvement were noted. In 9000 cases, only one case of lightheadedness and dizziness was noted. The clinical symptoms of cyanosis in this case were rapidly eradicated by the injection of methylene blue, the specific antidote for methemoglobinemia. Von Bohr and Eriksson[16] failed to demonstrate any instances of cyanosis in 6000 cases using prilocaine in the same doses, concentration, and volume as they had previously used in lidocaine-anesthetized cases. Eriksson[4] states that with doses of 600 mg or less clinical signs of methemoglobinemia are so slight that patients easily compensate for this minor reduction in oxygen-carrying capacity of the blood by slightly increased cardiac output. The methemoglobinemia does not seem to be a factor except in severely anemic patients with severe cardiac decompensation, but is contraindicated in patients with idiopathic or congenital methemoglobinemia. Bonica and associates[7] judged that at the dosage level of 600 mg, methemoglobin is a minor drawback to utilizing the drug in regional blocks and that, in the face of the extended duration of the anesthesia, it is a very useful agent and perhaps in many cases the drug of choice.

In the cases we have referred to here, the maximum dosage of prilocaine used was 400 mg (20 ml of 2% solution). At this dosage level, the duration and degree of anesthesia obtained is judged to be more than satisfactory for retinal detachment, anterior chamber, and photocoagulation cases.

### Summary

Prilocaine has enabled the performance of surgical procedures lasting as long as two hours and 20 minutes without the adjunctive use of epinephrine and without reinjection. In clinical practice, this agent has proven an excellent anesthetic for local blocks required in retinal, cataract, and anterior chamber procedures. The reduced toxicity, increased local diffusion, and greater duration of anesthesia allows the ophthalmic surgeon to select local anesthesia in patients with severe cardiovascular and respiratory problems. No instances of central nervous system toxicity,

cardiovascular decompensation, respiratory depression, or hypoxia have been noted. The reported surgical procedures were performed at an altitude 5000 feet above sea level (Denver, Colorado), and in many cases in this series, patients were not acclimated to this altitude. This is perhaps additional evidence of the inherent safety of this drug.

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# ADRENERGIC MYDRIASIS IN HORNER'S SYNDROME

## HYDROXYAMPHETAMINE TEST FOR DIAGNOSIS OF POSTGANGLIONIC DEFECTS

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In Horner's syndrome, the pupil often fails to respond normally to adrenergic mydriatic drops. Cocaine, for example, dilates the Horner's pupil poorly and epinephrine dilates it unusually well. The mydriatic response varies with the location of the lesion in the sympathetic pathway. In 1932, Foerster and Gagel[1] proposed the schema shown in Table 1 to localize the lesion in Horner's syndrome, and later a number of modifications were proposed.[2-5] In such tables the term "central neuron" denotes the sympathetic efferent pathway that originates in the hypothalamus and passes through the lateral part of the brainstem and cervical cord down to the $C_8$, $T_1$ level. It is not certain, however, whether this path actually is composed of a single neuron, or of a chain of neurons. The preganglionic neuron emerges from the spinal cord, passes over the apex of the lung and through the stellate ganglion, and ascends in the cervical sympathetic chain to synapse in the superior cervical ganglion. The postganglionic neuron to the iris follows the carotid plexus into the skull and is carried into the orbit with the ophthalmic division of the trigeminal nerve. The sweat fibers to the lower face follow the external carotid artery.

The cocaine and epinephrine tests are still used, but in practice they often fail to be sufficiently clear-cut to allow localization of the defect causing a Horner's syndrome.

In order to understand these tests it is necessary to have the mode of action of various adrenergic mydriatics clearly in mind.

*Cocaine*—When nerve impulses arrive at sympathetic nerve endings norepinephrine is released. Normally, some of this norepinephrine is taken up again by the axon and this terminates the adrenergic action. Cocaine blocks this re-uptake of norepinephrine into the axon and consequently the transmitter substance accumulates at the receptors of the effector cell. If the sympathetic pathway is interrupted, no norepinephrine is released at the neuro-effector junction and cocaine will have no mydriatic effect.

*Epinephrine and phenylephrine*—These are directly acting sympathomimetics. By virtue of their structural similarity to the natural transmitter substance (norepinephrine) they have a direct stimulating action on sympathetically innervated effector cells. When the sympathetic innervation is impaired, these cells become supersensitive to directly acting sympathomimetics and will then respond to weak and ordinarily ineffective concentrations of these drugs.

*Indirect-action adrenergic mydriatics*—There is a third class of adrenergic mydriat-

TABLE 1

SCHEMA* OF FOERSTER AND GAGEL[1]

| Agent | Central | Preganglionic | Postganglionic |
|---|---|---|---|
| Cocaine | Normal mydriasis | No dilation | No dilation |
| Epinephrine (1:1000) | No dilation | No dilation | Mydriasis |

* This schema of Foerster and Gagel (1932) suggested that the location of the lesion could be confidently identified using these mydriatic tests. This has proven to be false.

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ics: those which act indirectly by causing endogenous norepinephrine to be released from the sympathetic nerve endings. Such indirectly acting sympathomimetics do not, by themselves, stimulate the effector cell. They act on the presynaptic side of the neuroeffector junction to release norepinephrine from the stores in the nerve terminal. Hydroxyamphetamine 1% (Paredrine) belongs to this group of drugs and we chose to work with it (rather than with tyramine, amphetamine, or ephedrine) because it is already a widely used mydriatic and readily available. Using guanethidine, which depletes the axon's stores of norepinephrine,[6,7] we were able to show in the human eye that hydroxyamphetamine has, for practical purposes, an exclusively indirect mode of action (Fig. 1).

If the lesion causing a Horner's syndrome is central (brainstem or cord) or preganglionic (chest or neck), hydroxyamphetamine should cause normal mydriasis because the nerve endings of the postganglionic neuron are unimpaired. If, on the other hand, the lesion is postganglionic, some or all of the adrenergic nerve terminals will have degenerated, depending upon the extent of the damage. Consequently the stores of norepinephrine normally contained in them will be reduced or absent. When hydroxyamphetamine is instilled into the eye the pupil will therefore dilate incompletely or not at all.

According to our understanding of the action of these drugs, then, the cocaine dilation should be reduced or absent in any Horner's pupil, regardless of the site of the impairment. In contrast, hydroxyamphetamine should dilate the pupil normally in cases with central or preganglionic Horner's syndrome, but the reaction should be reduced or absent in cases with postganglionic Horner's syndrome. The following cases demonstrate that, with these drugs, a clear distinction between pre- and postganglionic lesions can indeed be made.

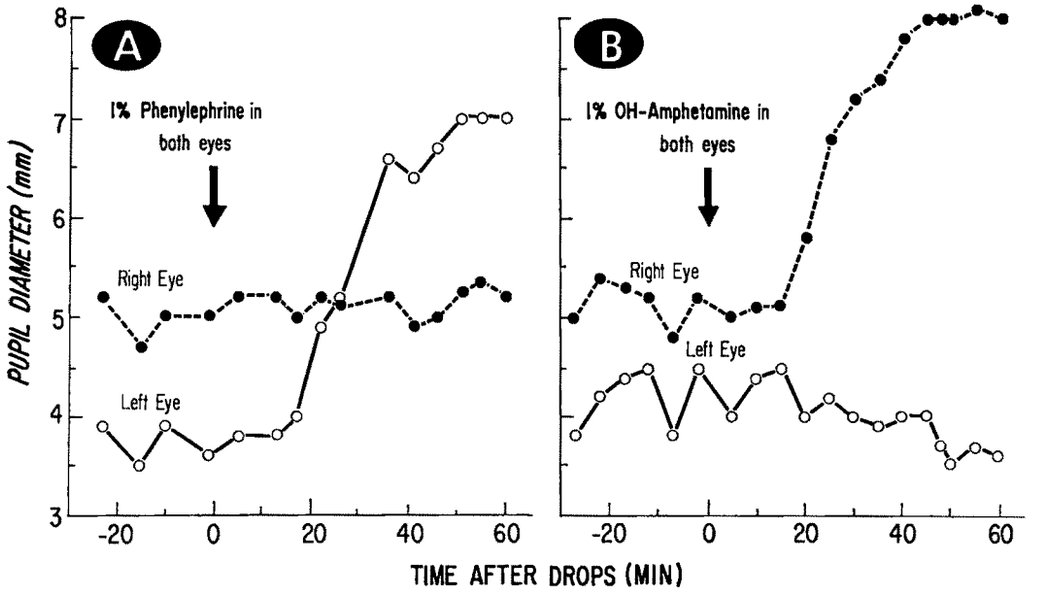



Fig. 1 (Thompson and Mensher). Experimental Horner's syndrome in the human eye, induced by the sympatholytic drug, guanethidine (5%), applied once daily to the left eye. (A) On the 10th day of treatment, this subject showed a dramatic supersensitivity of the pharmacologically sympathectomized pupil to 1% phenylephrine. No guanethidine drops had been placed in the eye since the day before; the eye was not irritated; the corneal epithelium did not stain with fluorescein. (B) After 16 days of guanethidine, OH-amphetamine 1% had no mydriatic effect upon the left pupil.

## METHODS

Thirteen patients with unilateral Horner's syndrome were seen in this series (Table 2). All were white; 10 were men and three, women; Their ages ranged from 32 to 74 years. Most were referred to the Ophthalmology Department at the University of Iowa Hospitals from the Neurology or Neurosurgery Departments, but six patients with surgical preganglionic lesions were sent from the Des Moines Veterans Administration Hospital Surgery Department through the courtesy of Louis Palumbo, M.D., Chief of Service. Pupillography was done using the Lowenstein-Loewenfeld electronic pupillograph. In addition, photographs of the pupils were taken with the Polaroid close-up camera (CU-5) with a three-inch lens. To

TABLE 2

DESCRIPTION OF CASES STUDIED

| Case, Years of Age, and Sex | History | Findings | Diagnosis | OH-amphetamine Response |
|---|---|---|---|---|
| 1. 32—F | Taking oral contraceptives; sudden onset of ataxia, vertigo, numbness of left face and right side of body | Blepharoptosis, miosis, and corneal hypesthesia on the left; sensory deficits | Lateral medullary syndrome (Wallenberg) | Dilation |
| 2. 54—M | Chronic hypertension; sudden onset of diplopia and vertigo | Left facial hypesthesia; right body hypesthesia; vocal cord paralysis; left blepharoptosis and miosis | Lateral medullary syndrome (Wallenberg) | Dilation |
| 3. 41—M | History of migraine; sudden onset of vertigo diplopia and ataxia and sensory deficit | Hypesthesia right side of face and body; Horner's syndrome and anhidrosis on the left | Superior cerebellar artery thrombosis | Dilation |
| 4. 49—M | Apical lung disease; bilateral progressive weakness and loss of sensation | Left Horner's syndrome | Suspected syringomyelia; apical lung disease, etiology unknown | Dilation |
| 5. 65—M | Intermittent claudication, acrocyanosis; bilateral, dorsal and lumbar sympathectomy; postoperative left blepharoptosis and miosis | Left Horner's syndrome; anhidrosis above nipples and below knees; later skin biopsy showed scleroderma | Surgical Horner's syndrome | Dilation |
| 6. 44—M | Intolerance to cold in arms and hands, vascular insufficiency; postoperative right blepharoptosis and miosis | Right Horner's syndrome with facial anhidrosis on right | Surgical Horner's syndrome | Dilation |
| 7. 70—M | Ten-year history of angina pectoris; left dorsal sympathectomy brought relief of precordial pain | Postoperative left blepharoptosis, miosis and anhidrosis of face, chest, and arm | Surgical Horner's syndrome | Dilation |
| 8. 38—M | Acrocyanosis; bilateral dorsal sympathectomy ($T_1$–$T_5$); postoperative right blepharoptosis and miosis | Right Horner's syndrome with anhidrosis above nipples | Surgical Horner's syndrome | No dilation |
| 9. 52—M | Numbness and cramps in right hand on exposure to cold; right dorsal sympathectomy ($T_1$–$T_5$) | Postoperative right blepharoptosis, miosis, and anhidrosis of right side of face, arm, and right upper chest | Surgical Horner's syndrome | Dilation |
| 10. 74—M | Five-year history of angina pectoris; atrial fibrillation; left dorsal sympathectomy for oppressive left precordial pain | Postoperative left Horner's syndrome | Surgical Horner's syndrome | Dilation |
| 11. 51—F | Left-sided headaches; diplopia for one year | Left abducens palsy; left Horner's syndrome; left corneal hypesthesia | Infraclinoid aneurysm of left internal carotid artery | No dilation |
| 12. 74—F | Intermittent right facial pain for seven years, accompanied by ipsilateral blepharoptosis, miosis, and nasal congestion | Persistent right Horner's syndrome | Cluster headaches with Horner's syndrome | No dilation |
| 13. 51—M | Trigeminal neuralgia and Horner's syndrome on left side treated with alcohol injection of gasserian ganglion | Hypalgesia and hyperesthesia of left face; left corneal hypesthesia; left Horner's syndrome | Trigeminal neuralgia with Horner's syndrome | No dilation |
| 14. 18—M | Auto injury at 13 months; crush injury to head and chest with over-riding occipital bones and pneumothorax; anisocoria noted postrecovery | Persistent right Horner's syndrome | Traumatic Horner's syndrome | No dilation |
| 15. 59—F | Auto injury at eight years of age with skull fracture; hospitalized at age 59 for cardiac surgery | Persistent Horner's syndrome | Traumatic Horner's syndrome | No dilation |
| 16. 8—M | Tractor crush injury to head and pelvis with basal skull fracture | Blind right eye, right abducens palsy and right Horner's syndrome; facial hypesthesia in first and second division of fifth nerve | Traumatic Horner's syndrome | No dilation |

reduce corneal reflections, 80% of the built-in ring flash was blocked out. The film used was Polacolor 75, type 108. Drugs used were: cocaine 5%, epinephrine HCl 0.1%, OH-amphetamine 1%, and phenylephrine HCl 10% viscous solution (Neo-Synephrine). One drop was placed in each conjunctival sac from standard plastic ophthalmic drop bottles. The pictures were taken in room light at 10-minute intervals with the patient focusing in the distance. Pupillary diameters were measured directly from these life-sized photographs to the nearest 0.1 mm, using a magnified scale (Mirroptic Comparator, National Tools). At least two days, sometimes four, were allowed to elapse between drug tests.

## Results

On the basis of the clinical picture, patients were separated into three categories according to the neuron presumably damaged (Table 3): central (Cases 1-3), preganglionic (Cases 4-10), or postganglionic (Cases 11-13). In Cases 14-16, Horner's syndrome was associated with head trauma.

All the patients demonstrated the characteristic pupillary features of Horner's syndrome: some tardiness of dilation in darkness after light reflexes and an increase of anisocoria after sudden noise. Otherwise, no pupillary motor defects were found in the pupillograms, even in the "central" cases.

Case 4 was classed with the preganglionic group on the basis of clinical judgment, even though the Horner's syndrome could have been due to a high cervical spinal cord defect. This patient was kept in the study because there was nothing to suggest that the postganglionic pathway was involved. Case 8 was observed to have a blepharoptosis and miosis after his thoracic sympathectomy and he may well have acquired a preganglionic Horner's syndrome at that time, yet in his drug tests he behaved in every way like the patients with postganglionic Horner's syndrome, failing to dilate to cocaine or to (OH-amphetamine, yet showing supersensitivity to phenylephrine. This patient may have had a pre-existing postganglionic sym-

TABLE 3

TABULATION OF THE MAXIMUM CHANGE IN PUPIL DIAMETER (IN MM) FOLLOWING INSTILLATION OF THE TEST MEDICATIONS

(mydriasis = +, miosis = −)

| Deficit, Patient Age, and Sex | Cocaine | | Epinephrine | | OH-Amphetamine | | Phenylephrine | | Diameter Before OH-Amphetamine | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | Horner's Pupil | Normal | Horner's Pupil | Normal | Horner's Pupil | Normal | Horner's Pupil | Normal | Horner's Pupil |
| Central neuron: | | | | | | | | | | |
| 1. 32—F | +1.5 | +0.5 | — | — | +1.0 | +2.0 | +2.0 | +3.5 | 5.0 | 2.5 |
| 2. 54—M | +1.3 | +0.6 | +0.3 | +1.1 | +1.5 | +2.5* | +3.5 | +4.3* | 3.0 | 2.5 |
| 3. 41—M | +2.3 | +0.7 | — | — | +1.7 | +2.8* | — | — | 5.5 | 5.0 |
| Preganglionic neuron: | | | | | | | | | | |
| 4. 49—M | +3.0 | +1.0 | 0.0 | +1.5 | +3.0 | +4.0* | — | — | 3.5 | 2.5 |
| 5. 65—M | +2.1 | +0.2 | −0.5 | −0.3 | +1.8 | +2.3* | +3.0 | +4.4* | 3.6 | 3.1 |
| 6. 44—M | +2.4 | +0.6 | −0.2 | 0.0 | +2.0 | +2.9* | +3.6 | +4.0* | 3.4 | 3.0 |
| 7. 70—M | +2.2 | +1.4 | 0.0 | −0.1 | +2.2 | +2.4 | +3.3 | +3.2 | 3.2 | 2.8 |
| 8. 38—M | +1.7 | 0.0 | −0.2 | 0.0 | +1.1 | +0.5 | +2.3 | +3.8* | 3.6 | 2.5 |
| 9. 52—M | +2.0 | −0.4 | 0.0 | +0.7 | +2.1 | +3.6 | +4.3 | +5.6 | 5.0 | 3.2 |
| 10. 74—M | +2.6 | −0.4 | +0.6 | +0.8 | +2.2 | +3.4* | +4.4 | +4.8 | 3.8 | 2.6 |
| Postganglionic neuron: | | | | | | | | | | |
| 11. 51—F | +1.6 | 0.0 | — | — | +1.4 | −0.4 | +2.3 | +3.8* | 5.0 | 4.2 |
| 12. 74—F | +1.4 | −0.4 | −0.2 | +0.6 | +2.7 | −0.2 | +4.2 | +5.0* | 3.5 | 2.8 |
| 13. 51—M | +2.5 | 0.0 | +0.5 | 0.0 | +2.0 | −0.7 | +2.5 | +4.5* | 4.0 | 3.0 |
| Trauma: | | | | | | | | | | |
| 14. 18—M | +1.8 | 0.0 | −0.4 | +0.4 | +1.8 | −0.8 | +3.8 | +3.2 | 5.9 | 5.0 |
| 15. 59—F | +0.8 | −0.3 | — | — | +0.3 | −0.6 | — | — | 7.7 | 6.0 |
| 16. 8—M | +1.4 | +0.8 | +0.2 | +0.3 | +1.6 | +0.5 | +2.1 | +4.2* | 4.1 | 2.7 |

* Tests in which the Horner's pupil "crossed over" and became the larger pupil.

pathetic defect, since there was an extensive sector heterochromia of the affected iris, or he may have developed a postganglionic lesion on top of the surgical preganglionic Horner's.

The mydriatic responses of the three patient groups are shown in Figures 3 through 5: cocaine (Fig. 2), hydroxyamphetamine (Figs. 3 and 5) and phenylephrine (Fig. 4). The individual responses, and the reactions to 1:1000 epinephrine, are given in Table 3. These values are all shown in millimeters of pupil diameter before and after the application of the drug, rather than as percentage increase of pupil size, because of the marked influence of mechanical factors upon pupillary movements.[8]

## Discussion

### Chief limitations of the cocaine test

If the sympathetic outflow pathway is interrupted at any level—that is, central, pre- or postganglionic—cocaine should have no mydriatic effect because in each case the flow of nerve impulses has been halted, and no norepinephrine is released.

Foerster and Gagel[1] reported a series of patients with anterior lateral cervical cordotomies whose Horner's pupils dilated normally to cocaine, yet our patients with medullary interruptions of the sympathetic path had Horner's pupils which dilated very poorly to cocaine. Similarly, Carmel[9] found reduced cocaine reactions in patients with lesions involving the ocular sympathetic pathways as rostral as the subthalamic area. These are not new observations; as early as 1906, Müller[10] reported a patient with Horner's syndrome associated with a brainstem stroke. The Horner's pupil dilated poorly to cocaine.

When the lesion is in the brainstem or spinal cord, cocaine mydriasis is usually impaired but not entirely abolished. This may be due to incomplete interruption of the descending sympathetic pathway. The cocaine test is a useful screening test to confirm the presence of a sympathetic pupillary deficit, but it will not indicate the location of the impairment.

### Chief limitation of tests for adrenergic supersensitivity

One drop of 1:1000 epinephrine had little or no mydriatic effect, even in cases with

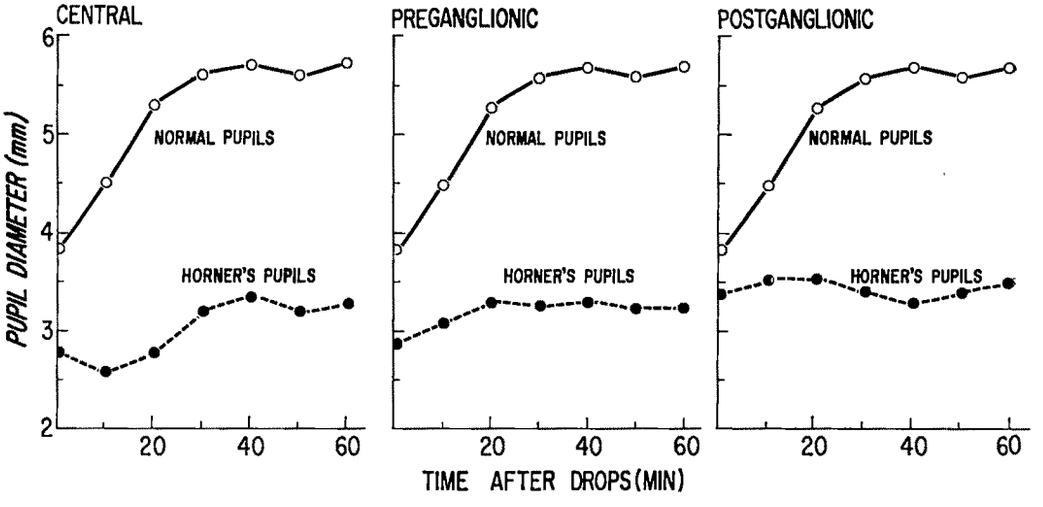



Fig. 2 (Thompson and Mensher). Summary of pupillary responses to cocaine in 12 patients with unilateral Horner's syndrome. The mean dilation curves are shown for each group. The unaffected pupils (12 patients, open circles) dilated normally. All of the Horner's pupils (three central, six preganglionic, three postganglionic) showed impaired dilation. There was a tendency for the most peripheral lesions to be associated with the least mydriasis.

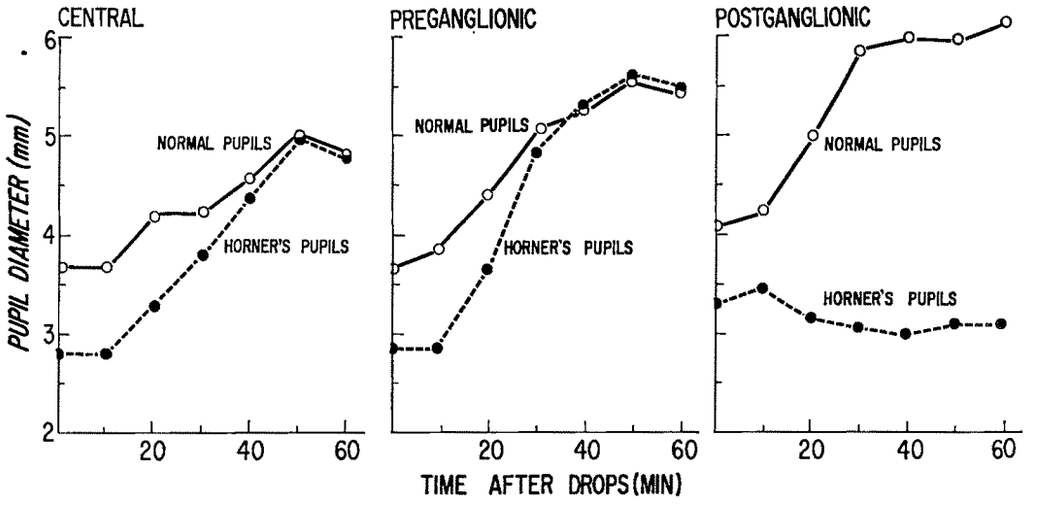



Fig. 3 (Thompson and Mensher). Summary of pupillary responses to OH-amphetamine in 12 patients with unilateral Horner's syndrome (three central, six preganglionic, three postganglionic; mean dilation curve was calculated for each group). The postganglionic group of Horner's pupils not only failed to dilate but actually became smaller during the test, partly because the patient sat in a chair for 90 minutes and became progressively more bored and sleepy, and partly because more light was entering the pupil of the other eye, which was dilating normally.

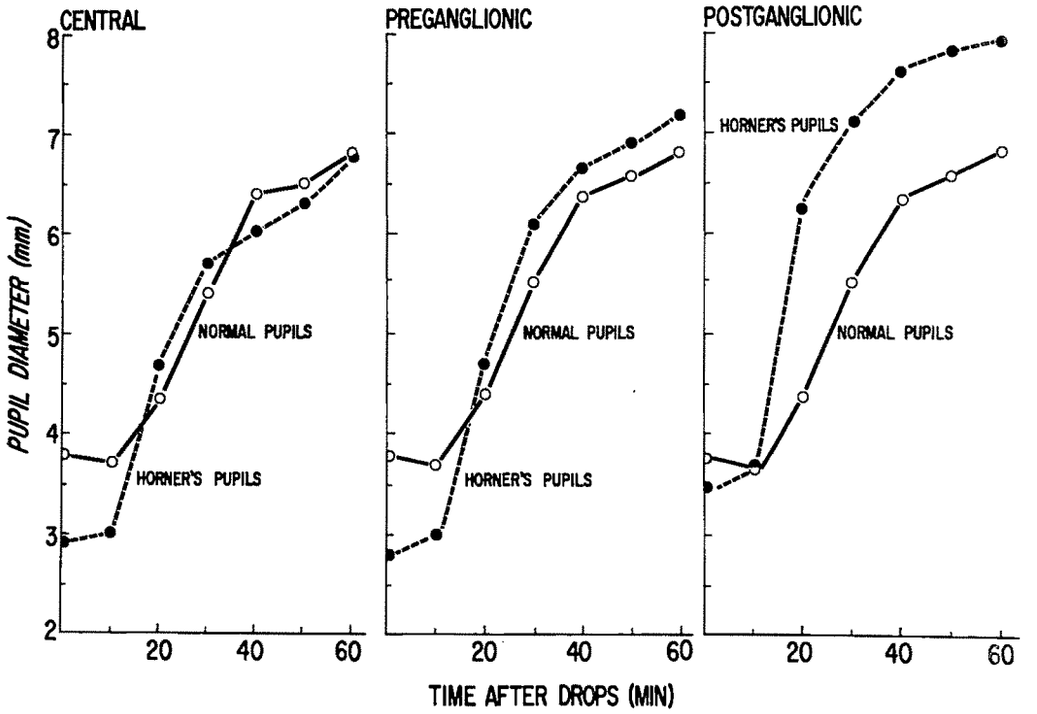



Fig. 4 (Thompson and Mensher). Summary of mydriatic responses to 10% phenylephrine in 12 patients with unilateral Horner's syndrome. The data were plotted as in Figure 2. Although all pupils showed a good dilation, the Horner's pupil always dilated sooner than the normal pupil. This supersensitivity of the Horner's pupil was most evident in the postganglionic cases.

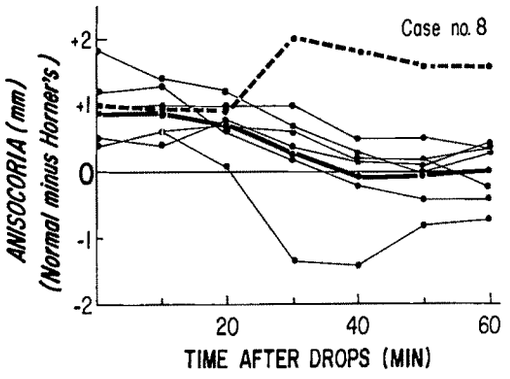



Fig. 5 (Thompson and Mensher). Case 8. Responses of the preganglionic group to OH-amphetamine in both eyes. The anisocoria due to the Horner's syndrome tended to disappear as the drug took effect. Some of the Horner's pupils in this group (heavy line is the mean) "crossed over" to become the larger pupils. Only Case 8 showed an increasing anisocoria due to failure of the Horner's pupil to dilate to OH-amphetamine.

postganglionic sympathetic lesions with demonstrable supersensitivity of the iris dilator. In many cases in the literature "maximal dilation" of the pupil in response to 0.1% epinephrine has been described.[5] But because it penetrates the cornea poorly and because there are great individual differences in sensitivity to epinephrine, even repeated instillations of this drug may give inconclusive results. Phenylephrine was, in our hands, a more dependable clinical tool than epinephrine for the demonstration of supersensitivity of the iris dilator to adrenergic drugs. The phenylephrine tests in this study were done with a very strong solution (10%, viscous), strong enough to cause extensive mydriasis in the normal pupil. Yet, in spite of this, a clear supersensitivity of the Horner's pupil was demonstrated in all the postganglionic cases. A weaker solution of phenylephrine, for example 1%, which has only a mild mydriatic affect on the normal pupil, provided a more dramatic demonstration of supersensitivity (Fig. 1).

When epinephrine or phenylephrine is used to distinguish a preganglionic from a postganglionic defect, a judgment must be made of the degree of supersensitivity of the iris dilator. In general, a denervated muscle (postganglionic lesion) is considerably more sensitive to these drugs than a decentralized muscle (preganglionic or central lesions),[11,12] and in the presence of marked supersensitivity a postganglionic lesion can thus be recognized.[13] However, a partial postganglionic lesion cannot be distinguished from a preganglionic lesion on the basis of supersensitivity to adrenergic drug tests; in both conditions the iris will show a slight supersensitivity. Similarly the effect of partial regeneration cannot be judged.

Tests for supersensitivity are also subject to false positive errors due to variations in penetration of the drug through an intact or damaged corneal epithelium.[14] The right iris must receive the same dose of the drug as the left iris or else erroneous conclusions about supersensitivity will be reached. This kind of mistake has been made in the past, for example in Löwy's test for facial nerve involvement.[15] In these cases, the mydriasis to 1:1000 epinephrine was mistaken for adrenergic supersensitivity. The mydriasis was, in reality, due to the penetration of the drug through a cornea which had been damaged by exposure.

### Advantages of the OH-amphetamine test

In contrast, the response to hydroxyamphetamine is not subject to errors due to interpersonal variations in drug sensitivity, or to somewhat uneven administration of the drops. The reaction depends upon the amount of norephinephrine available in the iris for release, and, provided that at least a dose sufficient to dilate the normal pupil is used, one eye may get a great deal more of the drug than the other without causing a difference in mydriatic response. Furthermore, if one pupil dilates poorly, this deficit cannot be due to a central or preganglionic lesion, because even complete excision of the preganglionic neuron does not impair OH-amphetamine mydriasis (Fig. 5). The poor

dilation indicates that there was insufficient norepinephrine available for release in that eye; and less than normal dilation therefore suggests a loss of postganglionic nerve fibers. This test thus provides a clearer distinction between pre- and postganglionic defects than is available with any other mydriatic test.

### Precautions

In all these tests, the drops should be instilled in both eyes, so that the reaction of the Horner's pupil can be compared with that of the normal eye. False results due to extremes of drug sensitivity can thus be avoided. Tests for supersensitivity can be done only when the corneal epithelium is intact in both eyes, so there should be no tonometry and no testing of corneal sensitivity before the drops are given.

For the cocaine test, it is important to remember that in some patients, especially those with dark irises, the response may be extremely slow. It is possible for cocaine mydriasis to take as long as two or three hours to become fully established, after which the mydriasis tends to be long-lasting. If, therefore, no dilation is observed in either eye after about 45 minutes, it is advisable to add more cocaine and to allow additional time.

Pretreatment with cocaine interferes with the action of hydroxyamphetamine (Fig. 6). For this reason, at least two days should elapse after cocaine administration before the OH-amphetamine reaction is tested.

### Summary

Adrenergic mydriasis was studied in a group of patients with unilateral Horner's syndrome. Cocaine dilated the central Horner's pupil poorly and the pre- and postganglionic pupils not at all. Phenylephrine (Neo-Synephrine) was used to demonstrate the supersensitivity of the denervated dilator muscles to adrenergic substances. OH-amphetamine (Paredrine) had a mydriatic action only when the postganglionic neuron was intact. OH-Amphetamine was shown to have an exclusively indirect mode of action. The cocaine test and the OH-amphetamine test cannot be done on the same day. The lat-

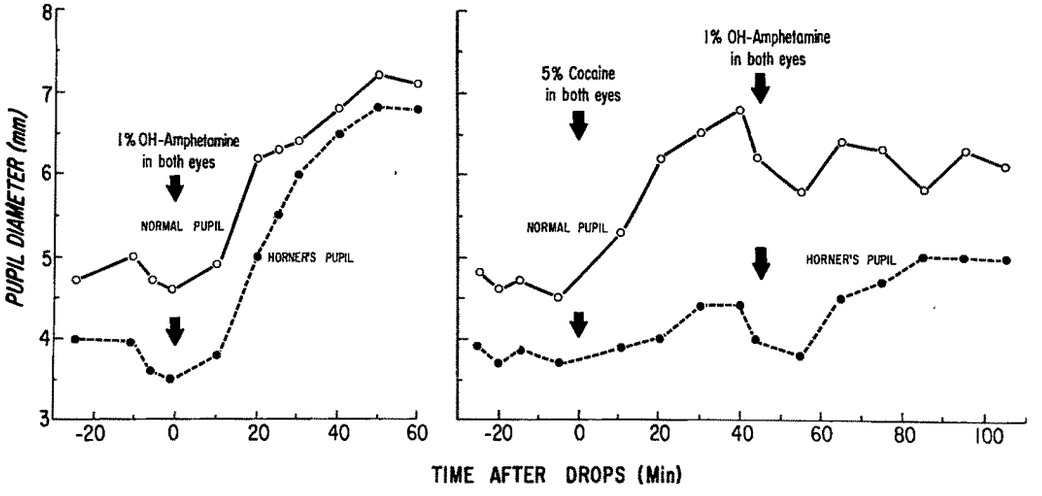



Fig. 6 (Thompson and Mensher). Case 8. This patient had had a blepharoptosis and miosis on the left side for 20 years dating from surgery for goiter on the left side of the neck. Both pupils dilated well to OH-amphetamine. Ten days later, cocaine dilated the Horner's pupil poorly. OH-amphetamine added on top of the cocaine failed to produce as much mydriasis as OH-amphetamine alone. This suggests that the cocaine and OH-amphetamine tests should be done on separate days so that they do not interfere with each other. Cocaine may block the uptake of amphetamine into the nerve endings.

ter test is offered as a new and better way to distinguish pre- from postganglionic sympathetic defects.

ACKNOWLEDGMENTS

We thank Mr. E. E. Brown for his skilled and patient technical assistance throughout this investigation and during the many preliminary experiments leading up to it.

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# GIANT CYST OF THE PARS PLANA

RICHARD STRANAHAN RUIZ, M.D.

*Houston, Texas*

Grignolo, Schepens, and Heath,[1] Okun,[2] and Allen, Miller, and Straatsma[3] state that pars plana cysts are formed by separation of the nonpigmented from the pigmented ciliary epithelium. They are usually confined to the temporal side of the globe, and usually conform to the individual ora bay, but may become confluent. These cysts are associcated with peripheral cystoid degeneration of the retina and can be considered a benign degenerative process increasing in incidence with age. There is often evidence of vitreal or zonular traction on the surface of the cysts, but holes in the walls of the cysts are unusual.

Possible causes for pars plana cysts include traction by the vitreous and zonules, secretory phenomena, vascular sclerosis, faulty embryologic development, and inflammation. This report describes a case of a giant pars plana cyst associated with other pars plana cysts of exceptionally large size.

## CASE REPORT

A 57-year-old white woman was seen for routine ophthalmic examination. Visual acuity was 20/15 in both eyes with correction and positive findings were confined to the posterior segments.

In the left eye, the temporal ora was irregular and unusual in appearance and there were multiple, large, irregular, highly-elevated cysts of the pars plana which overhung the ora region. In the inferior temporal quadrant, the pars plana extended posterior to the equator in a crescent shape and had the appearance of a huge ora bay. Overlying this large bay was a giant round cyst. No attachment was present from the vitreous or zonules to the surface of the cyst. The walls of the cyst were thin, gently undulating, and transparent, allowing easy visualization of the underlying retina and pars plana. The external wall of the cyst was composed of the posterior extension of the pars plana. The posterior extent of the cyst overhung the large ora bay and almost reached the visual axis. The anterior limit was lost from view over the anterior portion of the pars plana. No vessels were present on the surface of the cyst but normal retinal vessels could be seen on the surface of the retina under the cyst and extending up to but not over the large ora bay. Fluorescein did not accumulate in the pars plana cysts within one hour of intravenous injection. There was no visual field defect demonstrable

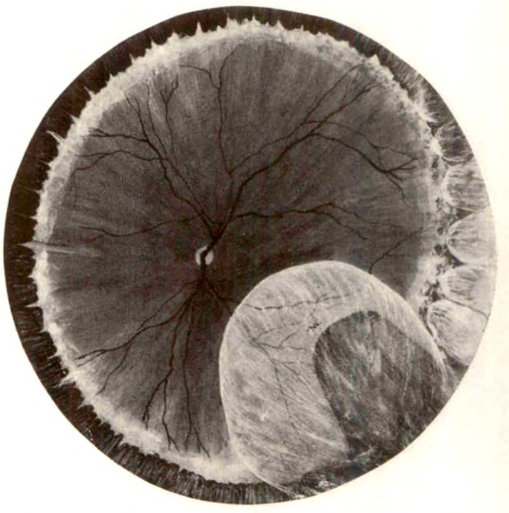


Fig. 1 (Ruiz). Fundus illustration of the left eye, showing giant cyst.

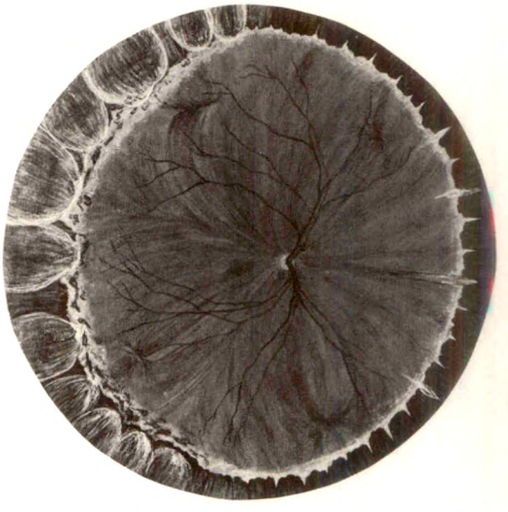


Fig. 2 (Ruiz). Fundus illustration of the right eye, showing large pars plana cyst and large ora serrata.

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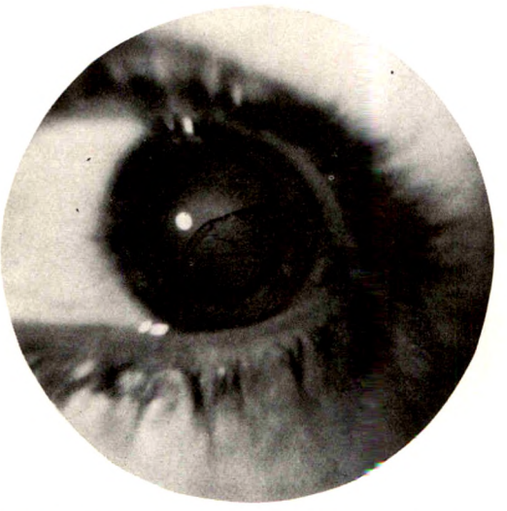


Fig. 3 (Ruiz). Slit-lamp photograph of giant pars plana cyst protruding into pupilliary opening.

with the Goldmann perimeter and no angle anomalies were present.

Examination of the right eye was negative except for multiple large pars plana cysts which overhung an irregular and anomalous ora serrata temporally.

No therapy was recommended. The fundus appearance is unchanged and the patient remains asymptomatic over a two-year period.


## Summary

A giant pars plana cyst was associated with additional unusually large pars plana cysts in a 57-year-old woman without symptoms and with no other abnormal ocular findings. In this case, the unusually large size of the cysts and their association with anomalies of the ora region suggested faulty embryologic development as the cause.



## Acknowledgment

This case was referred by Sylvan Brandon, M.D., fundus illustrations were done by Kay Smith, and photographs were taken by Antonino Deleza, both of Houston Eye Associates.


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## Ophthalmic miniature

As you ought not to attempt to cure eyes without head, or head without body, so you ought not to treat body without mind.

Socrates (c. 400 BC)

# NOTES, CASES, INSTRUMENTS

## METALLIC FOREIGN BODY REMOVED FROM TEAR DUCT

MOHAMMAD H. LASHKARI, M.D.
*Tehran, Iran*

A thorough survey of all available literature failed to reveal the report of a single case similar to that of my patient in whose right tear duct roentgenographic examination detected a metallic foreign body.

### CASE REPORT

A 22-year-old white woman complained of tearing from both eyes and of pain in the area of the tear duct of the right eye.

Her history showed that epiphora had developed after she had had smallpox at the age of four years. In 1967, at the age of 20 years, she underwent a dacryocystectomy on the left eye. The tear duct of the right eye was unsuccessfully probed in January, 1969. The pain worsened and a third ophthalmologist treated her for two or three weeks without discovering the cause of the pain.

When I first saw the patient in November, 1969, the right eye showed a scar in the region of the tear duct, caused by pericystitis, and the left eye showed the dacryocystectomy scar.

Laboratory examinations detected no abnormalities. X-ray studies, however, revealed a needle-shaped metallic foreign body (Fig. 1) that appeared to be about 1.0 cm in length. Its somewhat horizontal placement in the medial aspect of the right orbit suggested that it was located in the lacrimal canal.

The patient was admitted to the hospital. A dacryocystorhinostomy under local anesthesia made possible the removal of a slender piece of metal 10 mm in length (Fig. 2) which was identified as the broken-off tip of a probe.

The postoperative course was uneventful. The patient left the hospital in three days (Fig. 3) and, three days later, the suture was removed and the tear duct was irrigated. Recovery continued to be satisfactory. The most recent follow-up examination (Fig. 4) showed the patient to be in good condition. The epiphora had disappeared completely and she had no complaints.

### SUMMARY

Acting on x-ray evidence, the broken-off tip of a metal probe was removed in a dacry-

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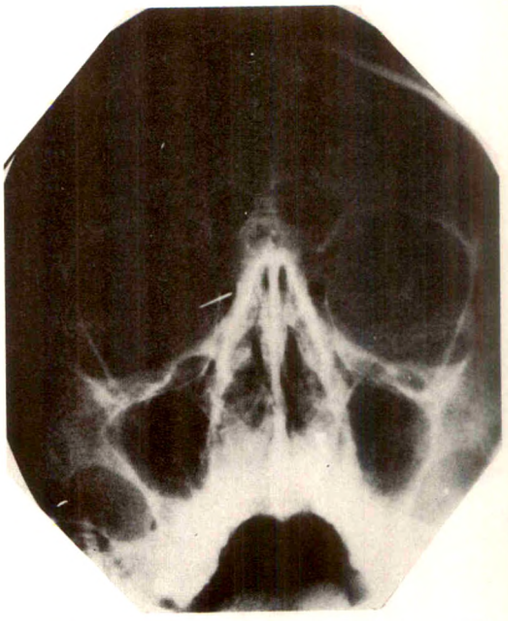


Fig. 1 (Lashkari). X-ray view of the slender metallic foreign body in the lacrimal canal.

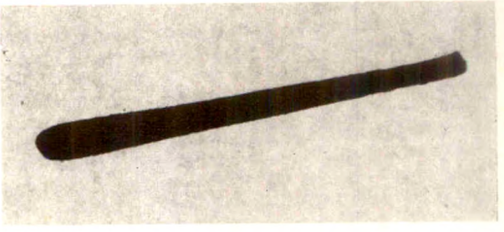


Fig. 2 (Lashkari). A 10-mm piece of metal was removed from the tear duct.



Fig. 3 (Lashkari). Appearance of the patient upon discharge from the hospital.



Fig. 4 (Lashkari). The patient shows a satisfactory result.

ocystorhinostomy from the tear duct of the right eye of a 22-year-old woman who had suffered from epiphora since childhood and who had had severe pain in the area of the tear duct following numerous probings of the lacrimal canal. Removal of the metallic foreign body relieved the pain and cured the epiphora.

ACKNOWLEDGMENT

I thank A. Fatemi, M.D., radiologist, and B. Parsa, M.D., for the x-ray studies and the use of laboratory facilities. I also thank Mr. Jahanfar for taking the photographs.

OPHTHALMIC MINIATURE

A child is taken, tied up in a small net, and placed towards the front part of the stage. A Sengalese comes in, bows, and slowly walks toward the place where the child is lying on the floor tied up in the net. He stoops over, looks intently at the child, and as he straightens up, the child's body is actually lifted from the floor and follows him as he walks several steps backward. He again stoops forward and allows the child to sink to the floor. To all appearances he has lifted the child from the floor with power from his eyes.

The child and the net are unprepared, but the Sengalese is prepared with a set of false eyes which he wears over his natural eyes. These are made of silver and are painted to resemble the human eye. These artificial eyes have aperatures which permit a perfect range of vision and are held in place by being inserted underneath the eyelids.

A very strong piece of silk twine (reaching below the knees) is fastened to each artificial eye, and a small strong hook is secured to the lower end of each piece of twine. As the Sengalese bends over and gazes intently at the child, he bends his knees and secretly inserts the hooks into the net entwining the child.

After the hooks are made fast, he slowly straightens up and bends backwards, and so causes the twine to rest upon his chest, thereby taking the actual strain from his eyes, and thus raises the child from the floor.

*Houdini on Magic*
Dover Publications, 1953

# MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

## AMERICAN OPHTHALMOLOGICAL SOCIETY MEETING—1971

The 107th annual meeting of the American Ophthalmological Society was held at the Homestead in Hot Springs, Virginia, May 24-26, 1971, under the direction of the president, Dohrmann K. Pischel. The weather was sparkling, the athletics stimulating, the papers interesting, and the ladies charming. The meeting was enjoyed by all.

More than half of the papers were devoted to various aspects of cataract or glaucoma. Lorenz Zimmerman gave the Verhoeff lecture, and described medulloepitheliomas, providing a masterful exposition of clinical observation and pathologic study, utilizing histochemical techniques, light and electron microscopy, and embryologic investigation. Most remarkable was the demonstration of striated muscle arising from the anterior extremity of the optic vesicle in the malignant form of this tumor. The paper will appear in an early issue of the JOURNAL.

Patz and Maumenee obtained good results with argon laser photocoagulation in serous fluid leakage beneath the neural epithelium in the macular region. Burian and Smith found that in many cases intermittent exodeviations became manifest when measurements were carried out 100 feet or more rather than 20 feet. Sharply demarcated destructive areas of chorioretinitis were observed in chronic granulomatous disease of children, a genetically determined disease due to a defect in leukocytes to destroy phagocytized microorganisms (Martyn, Lischner, and Harley, Philadephia).

A sharply defined central corneal opacity sensitive to chelation with EDTA was found in glaucomatous patients (Kennedy, Roca, and Landers, Rochester). Other members described similar opacities, not always associated with glaucoma.

Traumatic, secondary, and acquired cataracts in patients 15 to 40 years of age were easily aspirated, provided the nucleus was not hard (Maumenee and Barlow, Baltimore). Transformation of the mebomian glands into hair follicles to create an additional row of lashes on the posterior eyelid margins (distichiasis) was found in association with congenital lymphedema of the legs in three generations of a single family (Hoover and Kelley, Baltimore).

Injury from broken spectacles is more common in compound myopia than hyperopia and can be largely prevented by specifying heat-tempered glass of 3 mm or more or by using plastic lenses. Modification of the spectacle frame with a lip to prevent backward displacement of the lenses, careful study of the polarization pattern, and freedom from surface defects will additionally reduce damage (Keeney and Estlow, Philadelphia).

Soft contact lenses in keratoconus gave rise to surprising difficulties (McTigue and Townsend, Washington), a finding also described by several discussants.

At the annual business meeting, Trygve Gendersen, vice-president, succeeded Dohrmann K. Pischel as president. A. Gerard DeVoe was named vice-president, and Samuel D. McPherson, Jr., was re-elected secretary-treasurer. Clement McCulloch was re-elected editor of Transactions. William F. Hughes was named to the council, while Joseph A. C. Wadsworth completed his term on the council. During the meeting, seven associate members were named.

Frank Walsh awarded the Howe medal to C. Wilbur Rucker for his many contributions to ophthalmology, and he delighted the members and surprised Dr. Rucker by showing a number of photographs secretly provided by the Rucker children.

The annual business meeting was followed by the AOS picture show, with John Wend-

land showing spectacular motion pictures taken from a helicopter in the ski country of the Canadian Rockies.

The next meeting of the Society is May 29-31, 1972, at the Homestead.

Frank W. Newell

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## COMBINED MEETING OF THE EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY AND THE VERHOEFF SOCIETY

On the occasion of the 25th meeting of the Verhoeff Society and 10th meeting of the European Ophthalmic Pathology Society, a combined meeting of the two organizations was held in London, April 25-28, 1971. It was indeed a memorable occasion. Five years ago, an attempt was made to bring the two organizations together for the first time. This was thought to be so successful that an official combined meeting was organized for this jubilee occasion.

The meeting was held in the School of Pharmacy of the University of London. It was organized by Prof. Norman Ashton of London, aided by a most competent staff, and it was probably the best organized meeting I ever attended. It was so efficiently run that it was awe-inspiring! Particularly worthy of note was the spacious meeting room with 60 binocular microscopes, and the flawless projection of slides—everything ran without problems, and on time.

The emblem of this Congress (Fig. 1) was designed by Prof. Ashton and illustrates the two societies united by a semidecussation producing perfect binocular vision.

The meeting was opened by Prof. Casanovas of Barcelona, the chairman of the European Society. From then on each member presented his case and pointed out its unusual features. Usually, a lively discussion followed and thanks to a number of linguists in the audience all the remarks were readily translated into English. A total of 60 cases

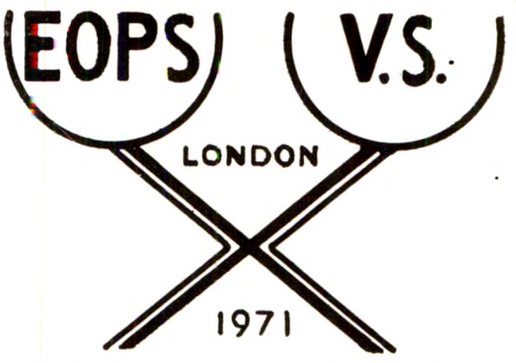



Fig. 1 (Blodi). Emblem of the Combined Congress designed by Prof. Norman Ashton, London.

were presented and discussed during the three days. Many of them will soon appear in print and will contribute to the advancement of our knowledge in ophthalmology in general and in ocular pathology in particular. A few most unusual and interesting cases should be mentioned here: an intraocular rhabdomyosarcoma (Nauman of Hamburg), the electron microscopic picture of asteroid hyalitis (Barry of Birmingham), the metaplasia of lens epithelium into bone (Landolt of Winterthur), and a retinitis pigmentosa with a choroidal hemangioma (Dhermy of Paris). The ocular manifestations of systemic diseases were especially well illustrated and some of them were described for the first time, such as: Kufs' syndrome (Font of Washington), mucopolysacchroidosis type 3 (Jensen of Copenhagen), Paget's disease of the bone (Gass of Miami), and coccidioidomycosis (Spencer of San Francisco). An interesting discussion centered around the proposed new classification of epithelial tumors of the ciliary body. Let's just hope that in the near future the proposal by Ry Anderson (Copenhagen) and the new classification as suggested by Zimmerman (Washington, D.C.) in his Verhoeff lecture can somehow be reconciled and combined.

The strenuous scientific meeting was complemented by a beautiful social program. The ladies had scheduled entertainment during the day, but the evenings were devoted to festive and impressive celebrations. On Sun-

day evening, the Verhoeff Society entertained the European Society at a cocktail party. This was followed by a dinner and then everybody departed by bus to visit Westminster Abbey. The Abbey was opened for the societies that night by special arrangement through the good offices of Prof. Ashton. The Dean and the Canons of the Abbey welcomed the group and guided them through the building. On Tuesday evening, the societies were invited by the Corporation of London to an official reception at Mansion House in the presence of the Lord Mayor. A number of the aldermen and other officials of the city of London were present and again acted as hosts, explaining the ceremony and the rituals. The reception was followed by a dinner given by the Department of Pathology of the Institute of Ophthalmology in London. This dinner was held at one of the old taverns on the Thames. The official banquet was held in the memorable Goldsmith Hall and Sir Stewart Duke-Elder and Derrick Vail were the special guests of the evening. The toast of the Verhoeff Society was given by Ted Sanders of St. Louis as the chairman of the group.

This combined meeting was certainly an unqualified success. It has helped bring together those ophthalmologists and pathologists who are interested in ocular pathology. Such an exchange of ideas and experiences can only be fruitful for the development of this branch of ocular sciences. In addition, it renews old friendships and establishes new ones. The language barrier was minimal and it is only to be hoped that this experience will lead to many more similar combined meetings of related societies.

F. C. Blodi

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OPHTHALMIC MINIATURE

"Light is a thing that cannot be reproduced" Cezanne said "but must be represented by something else—by colour. I was pleased with myself when I discovered that." This interchangeability of light and colour is similar to the modern notion of charges of energy. When Cezanne said "The painter is above all else an optic" he meant that the artist vibrates under the energy impulse of colour and translates the charge on to the canvas.

Liberman
*The Artist in Studio*

AMERICAN JOURNAL OF OPHTHALMOLOGY

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## THE CAUSE OF THE ARGYLL ROBERTSON PUPIL

An erudite and most valuable review summarizing the clinical and experimental bases for the hypothesized pathophysiology of the Argyll Robertson pupil has recently appeared.[1] It was stated that the pupillary light-near dissociation combined with miosis could be explained on the basis of a rostral midbrain lesion. The lesion needs to be located beyond the central hemidecussation of the light reflex path because impairment afferent to this decussation would involve both eyes, and, of course, the pupil of Argyll Robertson may be unilateral. A small lesion just rostral to the Westphal-Edinger nucleus —i.e., in the dorsal part of the midbrain tegmentum—would encounter both crossed and uncrossed pretectal fibers and thus abolish the light reflex. The near vision fibers which approach the nucleus slightly more ventrally would be spared, and the pupillary light-near dissociation would be explained.

It was further stated that the mechanism of the miosis must be sphincter contraction, cholinergically mediated, because (1) the miosis is pronounced, (2) the pupil does enlarge when the third nerve is blocked or

damaged, and (3) atropine, in the absence of iris damage, dilates the pupil.

Paralysis of the sympathetic was dismissed as causal because (1) miosis is more intense than that found in the usual Horner's syndrome, (2) no other signs of sympathetic paralysis are seen, (3) pupillary reflex dilation and dilation to cocaine can be shown to persist, and (4) there is no evidence for a pathway because the descending sympathetic runs quite lateral to the midline.

It was concluded that a destructive lesion of a supranuclear inhibitory pathway to the Westphal-Edinger nucleus must be the mechanism therefore of the Argyll Robertson pupil. But what is the nature of the inhibitory pathway?

I agree with this analysis that the miosis is cholinergically mediated and that the conventional sympathetic path descending in the lateral medulla is not involved. *Other central "sympathetic" fibers may well be, however.* In fact, there is a richly developed group of adrenergic fibers shown in the rat brain, containing the catecholamines norepinephrine and 5, hydroxytryptamine in large amounts, that are supranuclear and that contact specifically with the cells of the Westphal-Edinger group but not with those of the larger cells within the oculomotor complex; these, therefore, fit the requirement of a dorsomedial path (avoiding the ventral area described above).[2] Loss of this central "sympathetic" inhibitory path to produce the Argyll Robertson pupil is compatible with the site required by all the clinical and experimental data reviewed, and fits with the pharmacologic studies cited.[1]

The nature of the pathway interrupted in the production of the Argyll Robertson pupil would thus be a group of supranuclear inhibitory fibers, indeed, but a group of adrenergic fibers. The reproduction of a like miosis by the reserpine-induced depletion of norepinephrine in the central nervous system without peripheral (irridial) catecholamine depletion, as well as the miosis seen during sleep, are phenomena consistent with this concept. A search for these adrenergic fibers in higher animals should now be made so that the final chapter in the story of the Argyll Robertson pupil may be written.

The purpose of this note is to draw the clinician's attention to the new finding[2] of these adrenergic midbrain fibers[2] and to apply the results of the work to our understanding of the Argyll Robertson pupil.

Marvin L. Sears

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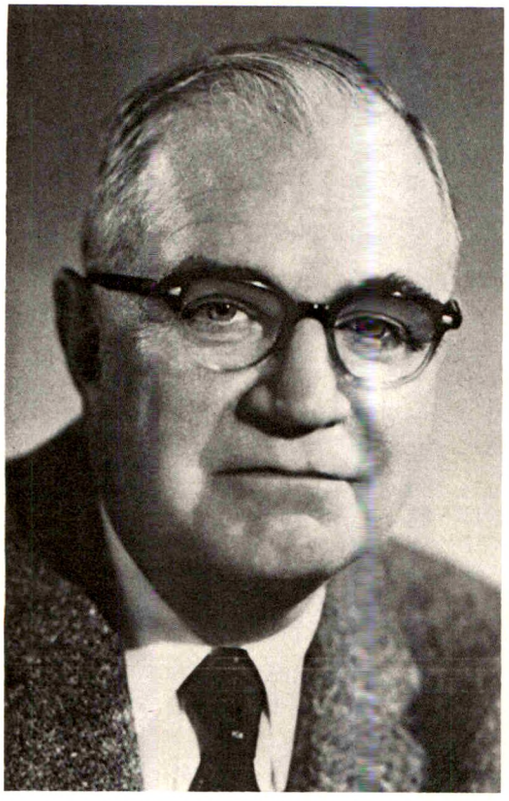
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## IN MEMORIAM

### WILLIAM A. MANN
### 1898–1971

William A. Mann, M.D., Secretary-Treasurer of the Ophthalmic Publishing Company, parent company of the AMERICAN JOURNAL OF OPHTHALMOLOGY, and a member of its editorial board since 1946, died May 18, 1971, in Chicago, Illinois. His death was sudden and unexpected; he and Mrs. Mann had planned to leave within the next several days on a leisurely drive to Hot Springs, Virginia, to attend the American Ophthalmological Society meeting and the annual meeting of the board of the Ophthalmic Publishing Company. On the evening of his death, he and Mrs. Mann left for a meeting of the trustees of Hadley School for the Blind, but returned home because of what was thought to be a slight indisposition.

Dr. Mann was Professor Emeritus of Ophthalmology at Northwestern University and Chairman Emeritus of the Department of Ophthalmology at Chicago Wesley Memorial Hospital and the Veterans Hospital at Hines, Illinois. He devoted his entire professional career to these institutions. He began as a clinical assistant at Northwestern



William Alfred Mann, M.D.

University in 1927, and ascended the academic ladder to become professor in 1949. He was acting chairman of the department of ophthalmology following Sanford Gifford's unexpected death in 1943, and managed the department until Derrick Vail became a professor in 1945. He was devoted and loyal to the department and did yeoman service in its organization and activities.

He served on the staffs of both Wesley and Passavant hospitals, and with the opening of the new Wesley Hospital in 1940, he became chairman of its department of ophthalmology and a consultant at Passavant. He began service with the United States Veterans' hospital in Hines in 1933 and became its chairman in 1946. He was responsible for instituting the residency program at both Wesley and Hines hospitals. In addition, he played an active role in the formation of the facility at Hines for training newly blinded soldiers.

The details of Dr. Mann's career are related in the special issue of the JOURNAL published in his honor in October, 1967. He attended the public schools in Chicago and Wilmette. He graduated from the University of Illinois and interned at Evanston hospital. His ophthalmic training was obtained at the University of Illinois and in Vienna.

In his early professional career he was active in the affairs of the Alpha Kappa Kappa medical fraternity. He served as president of the professional interfraternity council from 1933 to 1935 and was chairman of the medical interfraternity conference from 1947 to 1949. He was Grand Primerius of the Alpha Kappa Kappa Fraternity from 1949 to 1953, and again from 1963 to 1965. He also edited the Centaur, their official magazine, and served as president, grand vice-president, and grand historian. He was president of Omega Beta Pi, honorary national fraternity from 1932 to 1935 and served as president of Lambda Chi Alpha while attending the University of Illinois.

His scientific contributions were in two main areas, photography of the eye, and therapy. He was active in the development of color and infrared photography of the fundus and wrote his thesis for the American Ophthalmological Society describing an animal eye as a camera after Scheiner. He was active in the initial development of ACTH and the corticosteroids. For many years he gave a course in the optical correction of aphakia at the American Academy of Ophthalmology and Otolaryngology, from which he received its honor medal, and he wrote extensively concerning hysterical amblyopia.

His major love, however, was history. And at the time of his death he was historian of the Chicago Ophthalmological Society and had written extensively concerning the history of ophthalmology in the Illinois region.

He combined his interests in his final contribution, relating the history of photography in ophthalmology (Surv. Ophth. 1970).

Dr. Mann served as secretary-treasurer of the Ophthalmic Publishing Company from 1948 until his death. When he first took office the circulation of the JOURNAL was 4,000 and he saw it grow to more than 13,000. He also participated in the transition of the JOURNAL from a small enterprise managed principally in the office of its editor to an independent publishing group.

In reviewing Bill Mann's career, one is impressed by the number of successful enterprises with which he was associated: the training of nearly 100 ophthalmologists in residency programs he established at Wesley and Hines; the remarkable growth of the Hadley School for the Blind, where Bill served on the executive committee for many years; the extraordinary work done with rehabilitation of the blind at Hines Veterans Hospital; and the development of ophthalmology at Northwestern University.

He was a member of numerous organizations: American Medical Association, Illinois State Medical Society, Chicago Medical Society, American Ophthalmological Society, American Academy of Ophthalmology and Otolaryngology, Association for Research in Vision and Ophthalmology, American Association of Ophthalmology, Oxford Ophthalmological Congress, and American Society of Ophthalmology and Chicago Ophthalmological Society (President, 1946-47). He served as a member of the revision committee and as chairman of the panel on ophthalmology of the U.S. Pharmacopia from 1950 to 1960, and on the panel of ophthalmology from 1960 to 1965. He was a Congregationalist and a Knight Templar.

No description of Bill Mann's life would be complete without mention of the major role of his wife. They met at Northwestern University in 1928 where she worked in the social service department. In 1931, they were married, and since then she has played an active role in the things in which Bill was interested. Mrs. Mann is active in the Women's Board of Wesley Hospital, Northwestern University, and served as a trustee with him at the Hadley School for the Blind. She entertained his friends, colleagues, and residents at a sumptuous home in suburban Wilmette, and later, in their apartment overlooking Lake Michigan in Chicago. She traveled with him on his professional journeys and they were going to celebrate their 40th wedding anniversary at the Homestead during the meeting of the American Ophthalmological Society.

Chancellor Roscoe J. Miller of Northwestern University, a friend of Bill's since the time both were members of the faculty in medical school, stated in his eulogy, "Greatness is a quality that is measured by the impact a man creates on his family, his peers, his associates. Greatness in a man is found in the quality of his life, whether he be renown or unknown, popular or unsung, rich or poor, and the quality of a man's life is measured by the ways in which he comes to terms with life as that life unfolds itself to him."

The JOURNAL and its staff extend to Mrs. Mann, their three children, and seven grandchildren, their sincerest sympathies. We shall miss him greatly.

Frank W. Newell

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## HAIL AND FAREWELL

The executive family of the American Journal of Ophthalmology has suffered a grievous blow in the loss of William A. Mann. For 25 years as secretary-treasurer of the Ophthalmic Publishing Company, the parent of the JOURNAL, Bill had always given sound advice in the exercise of his calm judgement and great common sense. He was a good balance wheel, controlling my impulsive nature and quick decisions that might have been harmful. I am grateful for this.

Bill had an unusually sweet nature and this endeared him to a very large number of fast friends. He had great integrity and honesty. I shall miss him and will always cherish his loyal friendship.

Derrick Vail

## CORRESPONDENCE

### Gonioscopic evaluation of the narrow angle

Editor,

American Journal of Ophthalmology:

I found Dr. Gorin's article, Re-evaluation of gonioscopic findings in angle-closure glaucoma: Static versus manipulative gonioscopy (Am. J. Ophth. 71:894, 1971) of particular interest, as the gonioscopic evaluation of the narrow angle has been an area of considerable interest to me. Because many of my observations relate directly to this subject and differ somewhat from his I would like to make a few hopefully clarifying points:

1. Dr. Gorin states that static gonioscopy (applying the prism centrally to the eye without manipulation) elicits the "true state of narrowness of the angle." I do not believe this statement to be correct. Regardless which gonioprism is used (and the view of the angle will differ as it is dependent on which gonioprism one chances to use), the moment the gonioprism is applied to the eye inadvertant distortion—and therefore, inadvertant manipulation—occurs with alteration of the anatomic relationships and appearance of the angle. This has been described previously[1] and has been verified photographically.[2]

2. It has been well established that gross manipulation of the prism with pressure causes alteration in the normal anatomic relationships in the angle.[3] The more subtle and inadvertant distortion that occurs in the angle with manipulation of the prism, as occurs with sliding of the prism, has likewise been elucidated,[4] and it is indeed comforting that other gonioscopists such as Dr. Gorin are now recognizing and confirming these earlier observations.

I am always in favor of coining new terms when they add to our insight and understanding of a subject; however, I believe that all gonioscopy as presently performed results in distortion of the cornea and angle and therefore the words "static versus manipulative" has little meaning.

Stanley C. Becker
*St. Louis, Missouri*

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### Reply to Dr. Becker

Editor,

American Journal of Ophthalmology:

Dr. Becker seems to have overlooked the main purpose of my paper.

Teaching gonioscopy for the past 20 years, I have become concerned recently by the practice of undue manipulation of the gonioscopic lens leading to misjudgment of the narrowness of the angle. I was not interested in coining new terms. I used the term "static gonioscopy" as opposed to manipulative gonioscopy merely to emphasize the two different aspects of gonioscopy.

My paper had two main objectives:

1. To warn against undue manipulation in reaching a diagnosis of angle-closure glaucoma

2. To indicate that proper manipulation may assist in estimating the extent of synechial closure.

Experience with the Goldmann lens has shown that in most eyes gentle application of the lens to the center of the cornea causes hardly any change in the angle. The minimal change which occurs in a few eyes is of no clinical significance and does not depreciate the value of Goldmann lens gonioscopy in diagnosis and treatment of angle-closure glaucoma.

George Gorin
*New York, New York*

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### TREATMENT OF ANTERIOR CHAMBER OBLITERATION AFTER SURGERY

Editor,

American Journal of Ophthalmology:

Two days after a peripheral iris inclusion procedure for early, chronic, angle-closure glaucoma, a 64-year-old white housewife developed a stony-hard painful eye. The anterior chamber was obliterated. I pressed on the cornea 2 mm from the upper limbus with a Graefe muscle hook. The anterior chamber immediately reformed, pain was dramatically relieved and a small bleb was present. Two days later symptoms recurred and the same treatment was repeated with similar results. After six similar episodes, the apparent ball-valve action of the lens stopped and the chamber remained formed. There was no bleb and tension was 10 mm Hg. Subsequently, the opposite eye did well after a peripheral iridectomy, and in retrospect, that would appear to be the procedure of choice in this eye.

I submit this report in the hope that my colleagues, in a similar unhappy situation, may find similar relief for themselves and their patients by the use of this maneuver.

John A. Fusco
*Whittier, California*

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## BOOK REVIEWS

THE WORLD THROUGH BLUNTED SIGHT. By Patrick Trevor-Roper. New York, Bobbs-Merrill, 1970. Clothbound, 191 pages, table of contents, bibliography, list of illustrations, index, 83 black and white figures, 29 color figures. $12.50

This beautiful volume, with its profuse illustrations (29 in color) and its wealth of information, deals with the consequences of visual defects on the work and personality of artists, poets, authors, and composers. Every form of impairment is considered, including refractive errors, color perception deficiency, incipient cataract, strabismus, and aniseikonia. Psychedelic art and the art of the semi-sighted and blind are discussed. Examples and anecdotes are given: Probably because of his myopia, Gordon Craig introduced a new approach to stage design, emphasizing color and form over distracting details. Hitler's documents were prepared for him on a special large-type typewriter. El Greco's style has been attributed to astigmatism (Ahlström) or aniseikonia (Linksz), but x-ray examination of his work revealed that the elongations were secondarily imposed on the original sketches. It is suggested that Constable's color values probably stemmed from defective color discrimination. The amblyopic James Joyce compensated by stressing sound effects, alliteration, and musical words.

Trevor-Roper's encyclopedic erudition is revealed in the surprising incidental data: e.g., Lombroso, in 1883, was the first to note the usual association of right eye dominance with right-handedness; ancient Egyptian art indicated sex by color, males being red and females yellow; Lucretius recorded blindness from sun-gazing.

This unusual book should have a wide appeal, especially to those who would extend their ophthalmic insight beyond diagnostic and therapeutic needs.

James E. Lebensohn

MANUAL OF DISEASES OF THE CORNEA. By Merrill Grayson and Richard H. Keates. Boston, Little, Brown & Company, 1969. Clothbound, 311 pages, index, appendix, 236 figures in black and white, two figures in color.

This book was prepared to assist the resident in correlating information concerning the cornea. In this it wonderfully succeeds, for it presents a concise overview of a large variety of corneal diseases divided into those associated with primary corneal degenerations and those associated with systemic conditions. The text is richly illustrated and the references are current. A number of differential diagnoses are presented in table form. Treatment, which the authors plan to describe in another monograph, is not discussed. The text is highly recommended.

Frank W. Newell

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Cry-ophtalmologie. By P. J. Moreau, J. Haut, R. Alfieri, M. Brihaye, P. Payrau, Y. Pouliquen, D. Simatos, and P. Sole. Paperback, 746 pages, index of authors, alphabetical index of material, table of contents, 278 black and white figures. 100 francs

At the request of the French Ophthalmological Society, Profs. Moreau, of Dijon, and Haut, of Paris, with collaboration of six Gauls who are especially knowledgeable in cryo-ophthalmology, have prepared a report on all that has been done in this field. The documentation is extensive. More than 400 authors have contributed to the ophthalmic literature since 1918 when Schoeler reported causing an adhesion of internal tissues in the rabbit eye following the application of carbon dioxide snow to the sclera. The 1960s saw a deluge of papers on the subject, and I was surprised to learn that the first report in this decade on producing a chorioretinal adhesion was not by an American, but by a Russian. The book will be indispensable in the future for an author who wants to provide proper references for a cryosurgical paper.

There are six uneven parts to the book. The first is a basic science section on the physics of freezing and the response of cells to cold. This scholarly essay, by Mlle. D. Simatos, of Dijon, is couched in terms agreeable to the clinician. The second part, by Prof. Moreau, describes the instrumentation as well as the basic mechanics of cryosurgical devices. There follows a long section by Profs. Haut, Pouliquen, and Brihaye on biological experiments in the various tissues. Included are Brihaye's exceptional tables on the pathologic changes in sclera, choroid, and retina at every conceivable temperature and time.

The pathologic sections that were selected for reproduction are not as instructive. Nearly all were obtained after applications of degrees of cold in excess of that which causes total destruction of the rabbit retina, demonstrating that sclera survives almost any amount of freezing—for example, −160° C for 40 seconds.

The fourth part of the book is a short one on the treatment of skin lesions by cryosurgery. The fifth is a long report on therapy of the eye and tells about all the things for which cryosurgery is useful and a few for which it is not. Sixty pages are devoted to the management of cataract. The sixth part is about preservation of tissues, particularly cornea, and is 18 pages.

Most of the sections of the book conform to a pattern of presentation, reporting the literature in chronological order and precise form first. This is followed by a commentary from the author which is usually interesting and only occasionally indifferent. At the end of each part there is a brief resume in English. This is the 20th publication by the French Society since 1951. Profs. Moreau, Haut, and the collaborators deserve much credit for producing this handsome volume which continues a tradition of excellence.

Harvey Lincoff

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PHYSIOLOGY OF THE RETINA AND VISUAL PATHWAY, 2nd ed. Edited by G. S. Brindley. Baltimore, The Williams and Wilkins Company, 1970. Clothbound, 315 pages, table of contents, bibliography and index of authors, index of subjects, 64 black and white figures. $17.50

Unlike many second editions we see today, this book, first published in 1960, has been extensively rewritten, and it superbly integrates the older and classic lieterature with the exciting progress made in the field over the past 10 years.

The book remains a precise and concise introduction to the field, and it continues to be highly useful both to the serious student and to the expert. The selection of literature cited in the volume has been most carefully chosen, and, as noted in the preface, "most omissions are intentional." Although I (and many others in this field) would have selected additional experiments to mention, and would perhaps have omitted some of those cited, this book is extraordinarily comprehensive in the areas it covers and is probably the most objective work of its type available today.

In eight highly readable chapters (and in only 260 text pages!), the volume covers topics ranging from the photochemistry of the visual pigments to the psychophysics of visual thresholds and color vision. Along the way, the author discusses the electrical activity of the receptors and retinal nerve cells, the electroretinogram, and the structure and function of the higher visual centers.

One of the special charms and values of the book is the occasional section that points out the difficulties with the prevailing point of view on a particular subject; it discusses alternative hypotheses that cannot be dismissed at the moment (although many of us might like to do so). Two examples of such sections are entitled "Objections to the hypothesis of electrical signals" in the chapter on receptor activity, and "Function of centrifugal fibers to the human retina, *if they exist*" (italics mine) in the chapter on central pathways. There is also an excellent short chapter entitled, "Introduction to Sensory Experiments," particularly valuable for students, that assesses the role of various types of sensory experiments and provides a convenient classification of such experiments.

I highly recommend this book to any newcomer in the field of vision, or to anyone who would like to be brought up-to-date in this rapidly moving field. This book will be given a prominent place on my bookshelf, and I am confident it will be used often while we eagerly await the third edition. The price ($17.50) seems unnecessarily high, however, since the volume is only a little over 300 pages (including bibliography and index) and it contains only two half-tone reproductions. I would like to suggest that this book be purchased by every student in the field of vision, whether he is planning a career in the laboratory or in the clinic, but I am afraid that the price may put this splendid book beyond the reach of many.

John E. Dowling

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VISUAL PROSTHESIS—THE INTERDISCIPLINARY DIALOGUE. Edited by T. D. Sterling, E. A. Bering, Jr., S. B. Pollack, and H. G. Vaughn, Jr. New York, Academic Press, 1971. Clothbound, 382 pages, table of contents, list of participants, 105 black and white figures. $18.50

If man could replace vision, even in the primitive form, this would represent a significant triumph of his knowledge, scientific technology, and determination over the forces which govern many of his actions as a biological organism. During a two-day period in June, 1969, some 50 investigators in the fields of neurophysiology, neurosurgery, engineering, and computer science met at the University of Chicago and considered ways and means by which a functioning visual prosthesis could be produced. This book is a record of that conference, the second to be held

on this subject under the sponsorship of the Association for Computing Machinery.

Each of the individuals who contributed to the book are knowledgeable in their fields and most of them are presently working on one or more of the many aspects that could make artificial vision a possibility.

There was a free exchange of views, and much was learned from the discussions which took place between the formal presentations. The editors have de-emphasized extraneous material so that the reader can partake of some of the enjoyment and stimulation of the conference. The presentations of this conference have been arranged into a number of sections, each self-explanatory and each with editorial comment to serve as a guideline.

The phenomenon on which the possibility of a visual prosthesis is based has been considered until the present time more of a curiosity than a useful observation by most neurophysiologists. An illusion of a point or a surface of light is created when the cells in the visual cortex are stimulated. These sensations are called phosphenes. By implanting multiple electrodes in the visual cortex, it is possible to create an array of these phosphenes, or "lights." Perhaps, when combined with a clever system that arranges to turn on some and not others, this may be used to present images. Perhaps the phosphene phenomenon may offer a way of creating a practical visual prosthetic device. To bring the information to its present position required interdisciplinary cooperation in order to provide a common language so that dialogue could be pursued in a rewarding fashion.

A summary of the previously confidential first conference is included in this book as an appendix. This first conference served as a valuable sounding board for all good reasons why a useful visual device could not be built up to the time of that meeting, it also allowed a realistic assessment of the prospects of encouraging work that ultimately will lead to direct cortical stimulation. To Giles Brindley goes the credit for cutting through the skepticism and procrastination in order to present an actual demonstration of the feasibility of a direct implant. His work produced the stimulating discovery.

The conference on which this book is based was supported by funds from the NINDB Vocational Rehabilitation Agency and American Foundation for the Blind, as well as by interested friends.

Discussions at the second conference were based on observations of phosphenes in human subjects, and of brain stimulation. Stimulation studies done on the cortex in the geniculate bodies in the primary visual pathway and retina are reviewed. Discussions of ways of preprocessing visual information and potential designs of the system are analyzed in detail. Other possible approaches to aiding the blind are not neglected; some of these are a reading maching with tactile display, tactile visual synthesis, aids to mobility, and computer-aided generation of speech from the printed word.

It is difficult to decide how one should invest money for research to aid the blind. Perhaps much functional legal blindness might be overcome by greater expenditures for known remedies, such as ophthalmic therapy and surgery, better refraction, magnifiers, and counseling on the best use of existing aids. However, attention must be paid to psychological factors—the blind individual's acceptance of certain aids and the training entailed in their use. There does remain a strong case for the wisdom of expenditures for research and development on a broader spectrum.

Much consideration is given in this book to the propriety of prosthetic experiments on humans. There are some blind individuals who have given a great deal of thought to this, and some of them feel that the blind do not need a visual prosthesis as contemplated here. There are several discussions devoted to a thorough analysis of their position.

This text tells of a fascinating venture which will be of great interest to ophthalmologists, neurologists, neurosurgeons, neuro-

physiologists, biophysicists, computer scientists, engineers, and all those concerned with education and rehabilitation of the blind.

Irving H. Leopold

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FAMOUS HUNGARIAN OPHTHALMOLOGISTS. Edited by Magda Radnót. Budapest, Akadémiai Kiadó, 1970. Paperback, 31 pages, 12 black and white figures.

Hungary is a small country with a population of 10 million. Therefore, it is remarkable that such a small nation should produce as many leading figures in ophthalmology as this short monograph describes. The names of Imre, Hoor, Grosz, and Blaskovics are well known to ophthalmologists throughout the world. Their work and that of others named in this book serves as a stimulus to many young ophthalmologists in central Europe.

It is appropriate that such a volume should be published in preparation for the Fourth Congress of the European Society of Ophthalmology which is to be held in Budapest next spring. It demonstrates the important role Hungarian ophthalmology has played in Europe in the past 150 years and justifies the decision of the Congress to hold the meeting in Budapest. The editor should be congratulated for compiling this collection of biographies and providing us with this handsomely printed book.

Tibor G. Farkas

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LEPROSY IN FIVE YOUNG MEN. By George J. Hill, II. Denver, University of Colorado Press, 1971. Clothbound, 204 pages, table of contents, table of illustrations, Legend of Tables, glossary, index, references, 90 black and white figures. $8.00

In 1962 the National Institute of Health began a clinical study of leprosy in five selected patients. The major goal in bringing patients to the NIH clinical center was to stimulate the interest of medical and biological scientists in diverse fields in the hope that new ideas for research in leprosy might by forthcoming. The first objective was to describe in detail all the abnormalities present in the leprous patient. The present volume achieves that objective and concludes that leprosy can be effectively analyzed and treated in a general hospital or research hospital if precautions are followed similar to those for active tuberculosis.

Of specific interest to me were the findings confirming earlier observations that the nervous system, skeletal muscles, heart and lungs are spared in the vast majority of cases. Further, extensive skin lesions, neuropathy, fever and leonine facies may exist in patients with few lepra organisms. On the other hand, extensive involvement of viscera and other tissues may occur with only mild symptoms.

Ocular involvement is common. The five patients studied shed no new light on the occurrence or pathogenesis of ocular symptoms. One patient had a chorioretinitis related to toxoplasmosis. Others showed neural and follicular involvement on a leprous basis. Contrary to most experience, the two patients with lepromatous leprosy did not show anterior segment changes in the iris.

The book is handsomely printed and serves to alert the clinician to the fact that leprosy is a multisystem disease to be suspected in instances when the skin is discolored or hypesthetic, or whenever acid-fast bacilli are recovered which will not grow in culture.

M. L. Sears

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CONGENITAL AND PEDIATRIC GLAUCOMAS. By Robert N. Shaffer and Daniel I. Weiss. St. Louis, Mosby, 1970. Clothbound, 221 pages, 253 illustrations, color plate, subject index. $20.50

The book, in its first edition, is a timely and welcome addition to the libraries of pediatricians and ophthalmologists. The authors, through their vast personal experi-

ence, provide the reader with a thorough comprehensive survey of the field of pediatric glaucomas, emphasizing the clinically significant features and eliminating the clutter of the myriad "special" attributes that characterize each variant. This simplifying feature renders the book of great value to medical students and those in the health-related fields as well.

The book is organized in 12 chapters. The first two deal with general principals including classification of the glaucomas, the role of heredity and methods of diagnosis. The following six chapters discuss the genetically determined pediatric glaucomas: infantile glaucoma, primary glaucoma occurring after infancy, glaucoma associated with the phakomatoses, with mesodermal anomalies, with metabolic diseases, and with iris anomalies.

Nongenetic pediatric glaucomas (secondary glaucomas) are discussed in two chapters: one devoted to glaucoma associated with rubella infection; the last two chapters presenting medical and surgical therapy.

Throughout the entire book the lucid presentation of the authors is reinforced by elegant and effective illustrations that demonstrate clinical conditions, methods of investigation and therapy, light and electron microscopic findings, and photographic records of the optic disk and of fluorescein angiograms.

Mansour Armaly

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PHYSIOLOGY OF COLOR AND PATTERN VISION. By K. Motokawa. Clothbound, 283 pages, table of contents, list of references, author index, subject index, 137 black and white figures. $18.00

In his preface, Motokawa states that "The purpose of this book is to present the major studies on vision performed in our laboratory during the past 25 years, and also to describe in some detail related studies in other laboratories."

The book is divided into 11 chapters. The first three include discussions of the anatomy and electrophysiology of the retina and visual pathways, and a discussion of electrophysiologic correlates of some aspects of pattern vision. Chapters 4 through 10 are devoted to a detailed discussion of techniques, results, and interpretation of experiments utilizing electrical stimulation of the eye. Topics under discussion include induction, color vision, optical illusions, movement, and stereoscopic vision. Chapter 11 concludes with a number of models simulating various aspects of spatial and temporal visual function.

The book is physically attractive and well laid out. There is a 22-page reference section, but only a scant two-page subject index, which is not very useful. The author assumes that the reader has considerable knowledge of both vision and physiology. The book provides a comprehensive review of the utilization of the electrical phosphene to gain insight as to the functioning of the visual system, and will be of value to researchers specializing in visual function. It is not, however, a suitable teaching text.

Joel Pokorny

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THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 4th ed. Edited by Louis S. Goodman and Alfred Gilman. Toronto, MacMillan, 1971. Clothbound, 1794 pages, table of contents, index, 184 black and white figures. $25.00

It is 30 years since the publication of the first edition of this textbook, the "blue bible" of pharmacology. In the first two editions, the contents were provided solely by the two authors. In the third edition, published in the mid-1960's, it became, for the first time, a multi-authored work. The present fourth edition has undergone an updating of every chapter with respect to the mechanism of action, rational use of older therapeutic agents, and the addition of important new drug entities. The organization of the material in this text is similar to that of previous editions. Those who have read this book previously will find themselves on familiar ground.

This 1794-page volume tries to correlate pharmacology with related medical sciences, gives considerable attention to advances in medicine and interpretation of pharmacologic effects and actions leading to or influencing these advances. There has been a great effort made to help the reader evaluate promotional claims in published literature of new therapeutic agents. Many therapeutic agents that are in active use in each field are reported, with attempts made to reduce confusion, culling out those which are not well established, safe, and effective drugs.

There are many ways in which this tremendous compilation of data can be useful to the ophthalmologist. It provides fundamental knowledge of the action of agents which are employed by the ophthalmologist regularly or on rare occasions. He will have no difficulty understanding the mechanism of action of old and new agents, of comparing their chances for efficacy and toxicity. The specific fundamentals, essential for the proper use of any of these agents in all branches of ophthalmic therapeutics, are clearly defined.

The field of pharmacology has expanded rapidly in the past several decades, with remarkable advances in the various methods of testing for efficacy and toxicity. It is a Herculean task, and the two original authors, along with their fellow contributors, have brought order in a practical way into the therapeutic jungle.

Irving H. Leopold

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BECKER-SHAFFER'S DIAGNOSIS AND THERAPY OF THE GLAUCOMAS, 3rd ed. By Allan E. Kolker and John Hetherington, Jr. St. Louis, C. V. Mosby, 1970. Clothbound, table of contents, index, 495 pages. 383 black and white figures and six color plates. $25.00

The third and latest edition of this superb text has maintained the original purpose of the first: "to make available in one volume the current thinking on the pathogenesis, diagnosis and management of the glaucomas." The format of the current edition is the same as the second. First, there is a section on classification of the glaucomas. This is followed by a section on gonioscopy and one on tonometry and tonography. A fourth section deals with ophthalmoscopy and perimetry and includes a description of static perimetry. Sections on diagnosis and therapy, followed by separate chapters on medical and surgical techniques, complete a succinct but comprehensive review of the subject matter. An appendix includes examples of gonioscopic views, tables for tonometry and tonography, and examples of tonograms.

In a subject so complex, with ramifications that touch almost every specialty area of ophthalmology, it would be difficult for any reader not to find some areas of disagreement. These turn out to be of a minor nature when one considers the overall excellence of the volume. This book is a must for the office, library, and laboratory of every ophthalmologist. Together with lectures on glaucoma by Chandler and Grant, it forms the outstanding pair of textual contributions from this country on the subject of glaucoma.

Marvin L. Sears

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CLINICAL ASPECTS OF AUTONOMIC PHARMACOLOGY. By Paul Turner. Clothbound, 169 pages, table of contents, two indexes, 36 black and white figures, $7.50

The subject of autonomic activity and its relationship to the pathogenesis and treatment of disease has been revolutionized by two series of events which occurred in the past 10 years. The first has been an increase on understanding of transmitters, or their release and uptake. The second has been the introduction of compounds with relatively specific receptor blocking activity. The result of these new types of information has resulted in a change in thinking on autonomic pharmacology and has influenced the investi-

gations and treatment of many diseases.

The present text is an attempt to outline current concepts of autonomic pharmacology and its relationship to clinical methods in a manner which will be of value to both undergraduate and postgraduate clinical students.

The text is small, consisting of 169 pages. In an effort to reduce the volume of the text, the authors have deliberately written in an authoritative way without giving references for each statement of fact. However, each of the six chapters into which this book is divided is followed by selected references, usually to review articles which have appeared in the two or three years prior to the publication of this text.

In the introduction the authors review the physiology and pharmacology of the entire autonomic system. In the second and third chapters they specifically go into details of the actions of the parasympathometic and sympathometic drugs. Autonomic blockade is considered in one chapter. Autonomic activity in healthy man in a separate chapter and the autonomic activity and blockade in disease in another. In each of these the ocular effects are carefully considered. However, there are some omissions. For example, the ocular effects of noradrenalin are omitted as are those of isoprenalin and dopamine. At one point the author states that phenylephrine is an unsatisfactory mydriatic. In considering thymoxamine (Opilon), the author discusses his own work demonstrating its alpha blocking activity in man by local instillation into the cul-de-sac. These studies were done in 1968. However, he fails to mention the observations of Pau in 1955 in which he demonstrated thymoxamine to be a potent ocular adrenergic blocking agent and noted that this agent could block some of the actions of adrenalin as well as those of noradrenalin (Klin. Mbl. Augenheilk. 126:171, 1955).

The section on the autonomic activity and blockade in glaucoma is brief and does not present all of the information available in the literature. There are many discussions in this text which deal with ocularly oriented disorders—e.g., myasthenia gravis, familial dysautonomia, depression syndromes and anxiety states, Parkinson's disease, hyperthyroidism, and neurological alterations in pupillary function.

In addition, there are many diseases about which ophthalmologists are frequently consulted, such as pheochromocytomas, essential hypertension, cardiovascular system alterations, disturbances of the gastrointestinal and urinary tracts, and endocrine disorders other than diabetes and hyperthyroidism, and migraine. Ophthalmologists use these drugs probably more than or as much as any other specialty physicians. They will find a great deal of fundamental information included in this small text. It is possible that many ophthalmologists are not familiar with the diagnostic procedure known as the Loewi's test for acute pancreatitis which is discussed briefly. It is a test in which 0.10% solution of adrenalin, normally ineffective, is said to cause mydriasis. The pharmacologic basis of this test is not known.

At the present time, there are very few comprehensive reviews covering this entire and rapidly developing subject, but this text makes a noble effort.

Irving H. Leopold

# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ANNALES D'OCULISTIQUE

TREATMENT OF ABNORMAL RETINAL CORRESPONDENCE WITH PRISMS. (French) Adelstein, F. E. and Cupper, C. (University Ophthalmology Clinic Giessen, West Germany), Ann. Ocul. 203:445-457, May, 1970.

Seventy-eight children with ARC and strabismus completed treatment with surgical over-correction and/or correcting prisms Forty-seven of these eventually needed no prism, and 18 needed only weak prism in their glasses. (2 figures, 12 tables)—Kenneth Hovland

TREATMENT OF ACCIDENTAL PERFORATION OF THE HOST CORNEA IN LAMELLAR KERATOPLASTY. (French) Olteanu, M., Boeras, F. and Ciurea, V. (Central Military Hospital, Bucharest, Roumania), Ann. Ocul. 203:459-467, May, 1970.

Nine cases of lamellar keratoplasty (out of 847) developed accidental perforation of the host cornea during surgery. Several methods of closure were employed, including a new technique of piecing together corneal grafts. Favorable results were obtained in eight of the nine cases. (7 figures, 14 references)—Kenneth Hovland

MEDICAL TREATMENT OF ENDOCRINE EXOPHTHALMOS. (French) Lavergne, G. and Winand, R. (University Ophthalmology Clinic, Liege, Belgium), Ann. Ocul. 203: 469-472, May, 1970.

Using 80 mg of prednisolone per day, six of eight patients with severe endocrine exophthalmos were improved rapidly. The authors felt this was due to the immuno-suppressive action of the prednisolone. (8 references)—Kenneth Hovland

THE BATTERED CHILD SYNDROME OF SILVERMAN. OCULAR SIGNS. (French) Aron, J. J., Marx, M. F., Blank, R. D. and Luce, R. (Universitaire Necker-Enfants Malades), Ann. Ocul. 203:533-546, June, 1970.

This syndrome consists of multiple fractures of the long bones, combined with sequelae of subdural hematoma and scars in the skin and mucous membranes of the nose and mouth. Concurrent ocular signs are old chorioretinal lesions, heavily pigmented and retinal detachments. Eighteen case histories are reported in detail. All of them demonstrate severe ocular abnormalities. This syndrome has been related to neglect and disregard of infants and small children and has been described as the battered child syndrome. However, this theory could not be substantiated in all the patients discussed. As several children belong to the same family the possibility of a familial disposition to similar bone and eye changes should be considered. The etiology, therefore, is not established with certainty. (6 figures, 1 table, 11 references)—Alice Deutsch

RECOVERY FROM A PRIMARY ORBITAL NEUROBLASTOMA. (French) Firat, T. (Clinique d'Ophthalmologie, Ankara, Turkey), Ann. Ocul. 203:579-583, June, 1970.

Primary orbital neuroblastomas are very rare. Their origin probably is the ciliary ganglion. A bilateral neuroblastoma occurred in a 2½-year-old boy. He was treated by chemotherapy and radiotherapy. The chemotherapy consisted of Endoxan which was given IV for ten consecutive days, 100 mg the first day and 50 mg during the following nine days; 3600 r of x-ray were applied. The local tumor masses disappeared gradually. (2 figures, 9 references)—Alice Deutsch

ABNORMALITIES OF LOCATION AND DIVISION OF THE CENTRAL RETINAL ARTERY ON THE PAPILLA. (French) Bonamour, G. (Clinique Ophthalmologique de l'Hopital de la Croix-Rousse, Lyon, France), Ann. Ocul. 203:639-649, July, 1970.

Variations of the branching and direction of the central retinal artery on the papilla include protrusion into the vitreous; trifurcation; formation of a cross, star, or "parrot's ladder";

and nasal or inferior direction. With congenital malformations of these vessels, one should suspect further malformations of other internal carotid branches. (13 figures)—Kenneth Hovland

CRYOTHERAPY IN A CASE OF OCULAR ACNE ROSACEA. (French) Michail, S. (Strada Izvor, 90 Sector 6, Bucharest 5, Romania), Ann. Ocul. 203:669-672, July, 1970.

A 50-year-old patient with acne rosacea keratoconjunctivitis was treated successfully with cryotherapy at −70° C for 10 to 60 seconds and subconjunctival hydrocortisone.—Kenneth Hovland

OCULAR ANOMALIES OF THE PHENOTYPE DR (RING-CHROMOSOME D). (French) Saraux, H. Rethore, M. O., Aussanaire, M., Dhermy, P., Joly, C., Le Loch, J., Praud, E. and Lejenne, J. (Travail du Service d'Ophthalmologie de l'Hopital Trousseau), Ann. Ocul. 203:737-748, Aug., 1970.

The main ocular symptoms were microphthalmia and colobomatous cysts with cartilage formation between the retinal layers close to the optic nerve entrance below. The superior segment of the fundus was nearly normal. There was not any hyperplasia of the primary vitreous, persistance of the hyaloid artery or hyperplastic retinal dysplasia. The ocular abnormalities of this genetic defect therefore do not resemble those connected with the common signs of the typical trisomy 13. While the typical trisomy 13 shows a proliferation of the primary vitreous as well as the immature retina the ocular changes of the ring-chromosome 13 anomaly depends on a lagging invagination of the retinal layer of the primitive ocular vesicle just below the optic nerve entrance, at the location of the final closure of the fetal cleft. Other congenital anomalies found in this infant were hypertelorism, a prominent nasofrontal mass, large ears with a deep helix, agenesis of the thumbs and partial fusion of other fingers. Those findings are compared with the findings of 15 other cases of DR ring-chromosome; seven of these had ocular involvements. (11 figures, 18 references)—Alice Deutsch

OPTIC NEURITIS CAUSED BY DISULFIRAM. (French) Saraux, H. and Biais, B. (2 square Albain, 16 Paris), Ann. Ocul. 203: 769-774, Aug., 1970.

Disulfiram is used for the rehabilitation of alcoholics. It can produce a retrobulbar neuritis with a much larger central scotoma than the one observed with alcohol-tobacco toxicity. Improvement usually starts about one month after the drug is discontinued. (2 figures, 6 references)—Alice R. Deutsch

THE TREATMENT OF THE GONJEROT-SJOGREN SYNDROME. (French) Bonnet, M. (Clinique d'Ophthalmologique, Hopital de la Croix-Rousse), Ann. Ocul. 203:775-783, Aug., 1970.

Many of the classical treatments are effective and should still be used. This includes solutions of artificial tears and occlusion of the lacrimal puncta. In severe cases hydroxychloroquine has been used with subjective and objective improvement. Daily doses of 600 to 800 mg are given for twenty days each month up to three months. After this the doses are reduced to 400 mg. Careful evaluation of visual functions and fundus inspections are necessary if this medication is used. Assuming that the changes in the lacrimal glands are basically inflammatory injections of soluble corticosteroids are suggested, hoping that at least during the early stages the inflammation would abate and sclerosis be prevented. Two injections are given each week for one month, later one injection per week for three weeks, followed by one injection every two weeks and finally one injection a month. The results of this latter treatment were good in selected cases. (12 references)—Alice Deutsch

## ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

INFLUENCE OF 5-ETHYL-2-DEOXYURIDIN (EDU) ON THE REGENERATION OF THE EXPERIMENTALLY DAMAGED CORNEA. (German) Gauri, K. K., Malorny, G. and Rhiem, E. (Universitaets Augenklinik, 2000 Hamburg, Germany), Arch. Klin. Exp. Ophth. 179:287-293, 1970.

The regeneration of the rabbit cornea damaged by electrocautery was tested. The first group was treated with 0.5% EDU, the second

with 0.5% thymidin the third with 0.1% IDU and the fourth group with 0.9% NaCl solution. These solutions were injected subconjunctivally twice daily and dropped into the conjunctival sac four times daily. The corneas treated with EDU and thymidine solutions did not stain anymore on the fifth day in contrast to the corneas treated with IDU solution, which inhibits the regeneration of the corneal cells. (2 figures, 1 table, 15 references)—Walter Segall

A LIGHT- AND ELECTRONMICROSCOPIC STUDY OF AGE CHANGES IN THE HUMAN EYE. (German) van der Zypen, E. (Anatomisches Institut der Universitaet, 3550 Marburg a.d.Lahn, Germany), Arch. Klin. Exp. Ophth. 179:332-357, 1970.

Age changes begin between the twentieth and thirtieth year of life. In the beginning a marked increase in connective tissue can be seen; the electronmicroscope shows a fine granular amorphous mass which forces the muscle bundles apart. The circular muscle layer is affected first. After age 45 connective tissue pervades even the individual muscle bundles. At the age of 50 lipofuscin becomes deposited in the muscle cell. In old age the granular amorphous substance becomes replaced by coarse bundles of collagen fibers. The basement membrane of blood vessels in the ciliary body becomes stretched and degenerative changes occur in the endothelial cells. (2 tables, 35 references)—Walter Segall

COMPARATIVE EXPERIMENTAL INVESTIGATIONS OF THE RUPTURE RESISTANCE OF THE SCLERA AFTER APPLICATION OF ELECTROCOAGULATION CRYOTHERMY. (German) Matthaeus, W. and Dietze, H. (Augenklinik der med. Akademie, 8019 Dresden, DDR), Arch. Klin. Exp. Ophth. 179: 358-365, 1970.

The resistance of the sclera to rupture after electrocoagulation is reduced by about 60%. No reduction of the rupture resistance, however, resulted after cryothermy. (5 figures, I table, 26 references)—Walter Segall

## ARCHIVES OF NEUROLOGY

OPHTHALMOPLEGIA IN ACUTE POLYNEURITIS. Gibberd, F. B. (Department of Neurology, Westminster Hospital, London), Arch. Neurol. 23:161-164, Aug., 1970.

Six patients had acute polyneuritis and ophthalmoplegia. Two had complete internal and external ophthalmoplegia, two had complete external ophthalmoplegia but normal pupils, one had a partial external ophthalmoplegia and complete internal ophthalmoplegia, and one had partial internal and external ophthalmoplegia. It is concluded that the pupillary reaction can be lost during acute polyneuritis. (26 references)—Author's abstract

## ARCHIVES OF OPHTHALMOLOGY

INHERITANCE OF FUCHS' ENDOTHELIAL DYSTROPHY. Cross, H. E., Maumenee, A. E. and Cantolino, S. J .(Wilmer Institute, Johns Hopkins Hospital, Baltimore), Arch. Ophth. 85:268-272, Mar., 1971.

Two pedigrees contain seven individuals with documented Fuchs' endothelial dystrophy. A review of all previously reported familial cases reveals one pedigree with sufficient useful data for genetic analysis. Study of these three pedigrees together with segregation analysis suggests an autosomal dominant mutation as the most likely etiology, although alternative etiologies cannot be ruled out for other cases. An apparent female predilection for this disorder is present in the two reported sibships, which is similar to previously reported cases, but reduced penetrance of the gene cannot be documented. (3 figures, 8 references)—Authors' abstract

CONCOMITANT MEDIAL WALL FRACTURE AND BLOWOUT FRACTURE OF THE ORBIT. Dodick, J. M., Littleton, J. T. and Sod, L. M. (Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York 10021), Arch. Ophth. 85:273-276, Mar., 1971.

Medial wall fractures of the orbit should be considered a frequent component of the entity termed blowout fracture. Fracture of the medial wall without fracture of the floor did not occur in this series. Hypocycloidal tomography affords the best radiologic technique for diag-

nosing orbital fractures. (7 figures, 9 references)—Authors' abstract

SECONDARY AMYLOIDOSIS IN OCULAR LEPROSY. Rodrigues, M. and Zimmerman, L. E. (Armed Forces Institute of Pathology, Washington, D.C. 20305), Arch. Ophth. 85:277-279, Mar., 1971.

Deposits of amyloid were found in three eyes obtained postmortem from leprosy patients who had died in uremia from renal amyloidosis. We believe this may be the first report of ocular involvement in secondary amyloidosis associated with leprosy. (6 figures, 4 references)—Authors' abstract

"HOLES" IN BRUCH'S MEMBRANE. Friedman, E. and Strongin, M. (Boston University School of Medicine, Boston), Arch. Ophth. 85:280-282, Mar., 1971.

In a recent paper, "holes" were allegedly described in Bruch's membrane, and there has been speculation by the authors and others as to their significance. Utilizing both conventional histologic cross sections and flat preparations of the choroid, we find no evidence for the existence of such holes. Rather, it is clear that these apparent holes seen in flat preparations of the choroid are, in actuality, the lumina of the arterioles and venules supplying the choriocapillaris seen "end-on." (4 figures, 4 references)—Authors' abstract

HYDROPHILIC CONTACT LENSES IN CORNEAL DISEASE. Leibowitz, H. M. and Rosenthal, P. (University Hospital, 750 Harrison Ave., Boston), Arch. Ophth. 85:283-285, Mar., 1971.

A series of six patients illustrates that a hydrophilic contact lens may be fitted upon an edematous corneal epithelium containing bullae. The lens is well tolerated and may be worn continuously for prolonged periods without adverse effects. The lens produces a rapid and dramatic relief of pain and the accompanying symptoms of chronic bullous keratopathy. The lens itself produces no significant improvement in the clinical pathology of the epithelium, and symptomatic relief is directly dependent upon the lens remaining in place on the diseased cornea. (1 table, 3 references)—Authors' abstract

THE RECOVERY PHASE AFTER OCULAR HYPOTENSION INDUCED BY COMPRESSION. Schimek, R. A., Cooksey, J. C., Landreneau, M. and Steigner, J. B. (Oschsner Clinic, New Orleans, La. 70121), Arch. Ophth. 85:288-294, Mar., 1971.

As compression of the eye is often routine before intraocular surgery to help prevent vitreous loss, the duration of the resultant ocular hypotension is of clinical importance. Experimental and clinical studies after five minutes of compression of the eye demonstrated a homeostatic tendency for the untreated normal eye to recover most of its volume loss in 10 to 15 minutes. Continuation of pressure on the eye during early phases of intraocular surgery before the chamber is opened results in a more profound hypotension, but an increased episcleral bleeding tendency has been noted. Osmotic agents seem to increase the degrees and duration of ocular hypotension from compression. (8 figures, 4 tables, 8 references)—Authors' abstract

INTRAOCULAR INVOLVEMENT IN BURKITT'S LYMPHOMA. Karp, L. A., Zimmerman, L. E. and Payne, T. (Armed Forces Institute of Pathology, Washington, D.C.), Arch. Ophth. 85:295-298, Mar., 1971.

Burkitt's lymphoma, which is a poorly differentiated lymphocytic lymphoma with unique epidemiologic features and a characteristic clinical and histologic pattern, is the most common malignant tumor among children in tropical Africa. While the tumor frequently involves the orbit, it is not generally expected to involve the globe. The unique feature of, and sole reason for, recording the present case is the massive intraocular involvement. (5 figures, 25 references)—Joel G. Sacks

THE RUNNING INTERLOCKING SUTURE IN CATARACT SURGERY. Ryan, S. J. and Maumenee, A. (Wilmer Institute, Johns Hopkins University, Baltimore), Arch. Ophth. 85:302-303, Mar., 1971.

Utilizing the operating microscope, a limbal-based conjunctival flap is reflected, a corneal scleral groove created, and one or two sutures are preplaced. Following the opening of the eye, iridotomy, lens extraction, and filling the anterior chamber with air, the preplaced su-

ture is tied. A running interlocking 10-0 monofilament suture is then placed across the entire corneoscleral section, taking approximately 10 to 12 bites. (1 figure, 1 reference)—Joel G. Sacks

RETROBULBAR ADMINISTRATION OF STEROIDS IN HERPES SIMPLEX UVEITIS. Bohigian, G., Dawson, C. and Coleman, V. (University of California San Francisco Medical Center), Arch. Ophth. 85:320-328, Mar., 1971.

Efficacy of retrobulbar injections of dexamethasone on the von Szily model of herpes simplex chorio-retinitis was tested in rabbits. Herpesvirus hominis was injected into the anterior chamber of one eye of 45 rabbits. In each, a uveitis developed in the injected eye. In 36 animals a chorioretinitis appeared 7 to 12 days later in the uninoculated eye. Retrobulbar steroid or placebo therapy was begun in matched animals after clinical signs of the posterior chorioretinitis appeared. Eyes were examined daily by an observer not informed of the nature of the treatment. Clinical changes were correlated with photographs, viral titrations, and histologic examinations. A definite anti-inflammatory effect was observed during a short course of retrobulbar steroid therapy, although the final outcome was not altered. This short-term clinical improvement occurred without any significant increase in virus multiplication. (7 figures, 3 tables, 27 references)—Authors' abstract

THERAPY IN EXPERIMENTAL HYPHEMA. Masket, S., Best, M., Fisher, L. V., Kronenberg, S. M. and Galin, M. A. (Bird S. Coler Hospital, Welfare Island, New York 10017), Arch. Ophth. 85:329-333, Mar., 1971.

A radioactive assay technique was used to determine the rate of absorption of clotted and unclotted hyphemas in rabbits. Unclotted blood in the anterior chamber was absorbed at a significantly more rapid rate than clotted blood. Treatment of rabbits with clotted hyphemas with intravenous infusions of hyperosmotic urea and mannitol markedly enhanced blood resportion. Subconjunctival injections of methylprednisolone before clotting occurred resulted in poor clot formation and retraction, and thereby enhanced blood resorption. Subconjunctival injections of methylprednisolone after clot formation slightly decreased blood resorption rate. (5 figures, 20 references)—Authors' abstract

OCULAR DIATHERMY AND CRYOCOAGULATION. Miller, J. B. (1127 Wilshire Blvd., Los Angeles 90017), Arch. Ophth. 85: 339-349, Mar., 1971.

A comparison between diathermy and cryotherapy was made in lesions which were placed in single eyes of adult, albino rabbits. The effects on both the retinal and choroidal vessels were stressed. Moderate to heavy dosage was used. Cryoprobe application caused immediate retinal and choroidal hemorrhage which slowly resorbed during the first week. Diathermy caused a hemostatic, coagulative effect on the retinal vessels. Diathermy to the choroid caused initial hemorrhage and hyperemia which was distributed to a circumferential pattern around a central, avascular, coagulated area. Both diathermy and cryotherapy caused obliteration of the smaller retinal and choroidal vessels. Diathermy resulted in a more adherent and "stickier" early chorioretinal adhesion than cryotherapy. Heparin had little effect on the hemorrhagic tendency of either diathermy or cryotherapy. (17 figures, 1 table, 17 references)—Author's abstract

TOPICALLY APPLIED STEROIDS IN ACTIVE HERPES SIMPLEX KERATITIS. Takahashi, G. H., Leibowitz, H. M. and Kibrick, S. (University Hospital, 750 Harrison Ave., Boston 02118), Arch. Ophth. 85:350-354, Mar., 1971.

Topical administration of medrysone 1.0% produced a detrimental effect on active infection of the corneal epithelium by herpes simplex virus. Treatment with this drug resulted in a keratitis that was more severe in its clinical characteristics and ran a more prolonged course than the disease observed in control animals. A ten-day course of therapy also resulted in a prolongation of the period during which virus could be cultured from the eye. The undesirable effects produced by medrysone 1.0% were not as pronounced as those which followed administration of dexamethasone phosphate 0.1%. (4 tables, 11 references)—Authors' abstract

MULTILINE ARGON LASER. Behrendt, T. (Thomas Jefferson University, 1025

Walnut St., Philadelphia 19107), Arch. Ophth. 85:355-358, Mar., 1971.

Continuous argon and krypton gas laser sources are available commercially. By their nature they are bulky and relatively unmanageable in optical systems designed to focus on ocular tissues. By taking advantage of a simple geometric design of placing mirrors at diagonals of parallelograms, it is possible to provide maximum flexibility and minimum energy loss into such a system. The device is useful for producing microlesions in retinal vessels. (10 figures, 3 references)—Authors' abstract

TRANSIENT CORTICAL BLINDNESS AND CEREBELLAR ATAXIA ASSOCIATED WITH MUMPS. Davis, L. E., Harms, A. C. and Chin, T. D. Y. (Ecological Investigations Program, 2002 W. 39th St., Kansas City, Kansas 66103), Arch. Ophth. 85:366-368, Mar., 1971.

Visual impairment is an unusual complication of mumps and may be secondary to pathological conditions in several places along the optic pathway. Cortical blindness, however, is an extremely rare complication. A 25-year-old woman suddenly developed meningitis, cortical blindness, and cerebellar ataxia during an acute episode of parotitis associated with rise in mumps neutralizing antibodies. The patient recovered completely with only supportive care in six days. (1 figure, 10 references)—Authors' abstract

PIGMENTARY EPITHELIOPATHY AND ERYTHEMA NODOSUM. Van Buskirk, E. M., Lessell, S. and Friedman, E. (Boston University Medical Center, 80 E. Concord St., Boston 02118), Arch. Ophth. 85:369-372, Mar., 1971.

A young woman with erythema nodosum demonstrated the clinical and fluorescein angiographic findings of acute posterior multifocal placoid pigment epitheliopathy. The possibility of a relationship between the two disorders is raised. The fluorescein angiograms seemed suggestive of choroidal vascular disease rather than of a primary pigment epitheliopathy. (3 figures, 5 references)—Authors' abstract

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## BRITISH MEDICAL JOURNAL

LASER IRIDOTOMY. Perkins, E. S. (Institute of Ophthalmology, London), Brit. Med. J. 1:580-581, 1970.

A ruby laser has been used to produce a permeable lesion in the iris to establish a communication between the anterior and posterior chambers. In a preliminary study in nine patients the technique gave satisfactory results in the prophylactic treatment of four cases of incipient closed-angle glaucoma and of two cases of iris bombe following uveitis. (4 references)—Authors' abstract

MIOSIS DURING L-DOPA THERAPY. Spiers, A. S. D., Calne, D. B. and Fayers, P. M. (University College Hospital, London W.C.1.), Brit. Med. J. 2:639-640, 1970.

The pupillary diameter of 11 patients with Parkinson's disease was significantly decreased four hours after ingestion of L-dopa. It is suggested that this miosis may be caused by diminished noradrenaline output at sympathetic nerve endings, or alternatively by an action on the central nervous system. (1 figure, 19 references)—Authors' abstract

## CANADIAN JOURNAL OF OPHTHALMOLOGY

COATS' DISEASE, DIAGNOSIS AND TREATMENT. Harris, G. S. (Department of Ophthalmology, University of British Columbia, 2550 Willow Street, Vancouver, 9, Canada), Canad. J. Ophth. 5:311-320, Oct., 1970.

Twenty-three patients with Coats' disease were studied. The presence of the abnormal retinal vessels is an important point in distinguishing this condition from retinoblastoma. About half the patients were felt to be treatable and of these, more than half had their disease cured or arrested. Destruction of the anomalous vessels is necessary and this usually can be most readily accomplished with the photocoagulator. If the anomalous vessels are elevated by a serous detachment, a posterior sclerotomy must be performed first. The insertion of a scleral buckle during this procedure is sometimes the most effective way of securing effective photocoagulation. Once the anomalous vessels are destroyed, the subretinal

exudates and serous fluid disappear. Once fibrosis, pigment hyperplasia or hemorrhage have occurred, the condition is not reversible and treatment can only be directed at delimiting the extent of the disease. (11 figures, 5 tables, 12 references)—R. Theodore Goldberg

HEMORRHAGE ON THE DISC—A SIGN OF ACUTE ISCHEMIC OPTIC NEUROPATHY IN CHRONIC SIMPLE GLAUCOMA. Begg, I. S., Drance, S. M. and Sweeney, V. P. (Department of Opthalmology, University of British Columbia, Vancouver 9, British Columbia, Canada), Canad. J. Ophth. 5: 321-330, Oct., 1970.

Four patients with chronic open-angle glaucoma developed a hemorrhage on a sector of the disc accompanied by the occurrence of a corresponding absolute scotoma in the Bjerrum area, which probably represented an acute ischemic change at the optic nerve head. This ischemic optic neuropathy was symptomless, discrete, recurrent, sometimes bilateral, and produced a progression of field loss. It was probably associated with small vessel disease and occurred at levels of intraocular pressure which were normal or just above normal, and with or without adverse perfusion pressure at the optic nerve head. (11 figures, 9 references)—R. Theodore Goldberg

CONGENITAL FIBROSIS SYNDROME. Crawford, J. S. (Department of Ophthalmology, The Hospital for Sick Children, 555 University Avenue, Toronto 101, Ontario, Canada), Canad. J. Ophth. 5:331-336, Oct. 1970.

Sixteen patients with congenital fibrosis of all the extraocular muscles and the levator muscle, are reviewed. There is frequently a family history with autosomal dominant inheritance. All 16 held the head tilted backward with the chin elevated and all had bilateral hypotropia with eyes fixed in a downward position 20 to 30 degrees below the horizontal. Eleven patients showed jerky convergent movements on attempted upward gaze. In most cases, vertical muscle surgery on the recti did not elevate the eyes enough, and the author recommends a 6 mm recession of the inferior rectus and resection of the superior rectus to obtain best results. Eleven of 16 patients had fascia lata suspension operations for ptosis despite the absence of Bell's phenomenon. The lids were raised above the pupils, but not as high as in those cases where a Bell's phenomenon was present. Surgery can offer cosmetic improvement and symptomatic relief from fatiguing head positions. (6 figures)—R. Theodore Goldberg

SEVERE APLASTIC ANEMIA AS A COMPLICATION OF ACETAZOLAMIDE THERAPY. Rentiers, P. K., Johnston, A. C. and Buskard, N. (Department of Ophthalmology, University of British Columbia, 2550 Willow Street, Vancouver 9, British Columbia, Canada), Canad. J. Ophth. 5:337-342, Oct., 1970.

A patient with chronic open-angle glaucoma who was treated with Diamox for seven months, developed severe aplastic anemia. The ophthalmologist should be alert to the symptoms and signs of aplastic anemia, which are weakness, pallor, hemorrhages, ecchymoses, and a decreased resistance to infections. The peripheral blood shows depression of red and white blood cells and platelets. The marrow is fatty and hypocellular. During this patient's severely anemic period, the relative ischemia of the optic nerve head allowed further nerve fiber bundle infarction to occur despite normal intraocular pressures. (5 figures, 2 references) —R. Theodore Goldberg

PEDUNCULATED MALIGNANT MELANOMA OF CONJUNCTIVA. Watson, A. G., Campbell, J. S., Tolnai, G. and Hill, D. P. (Dept. of Ophthalmology, Ottawa General Hospital, Ottawa, Canada), Canad. J. Ophth. 5:386-391, Oct., 1970.

There is a predilection of precancerous melanosis and junctional nevi for the limbic and caruncular areas. Pedunculation suggests a good prognosis generally and extensive local excision of such lesions may be indicated in exceptional cases where there is pedunculation and no sign of spread of the neoplasm. (6 figures, 22 references)—R. Theodore Goldberg

## JAPANESE JOURNAL OF OPHTHALMOLOGY

ELECTRON MICROSCOPIC OBSERVATIONS ON REACTIONS OF RETINAL MULLER CELLS UNDER PATHOLOGICAL CONDITION. Uga, S.

and Katsume, K. (Department of Ophthalmology, Kyushu University, Fukuoka), Jap. J. Ophth. 13:223-236, Oct-Dec., 1970.

Under certain conditions Muller cell processes may penetrate the inner limiting membrane and grow into the vitreous. The Muller cells may also phagocytose disintegrated retinal cells. (15 figures, 26 references)—Paul A. Hein, Jr.

ULTRASTRUCTURAL OBSERVATION ON THE CORNEA OF HURLER SYNDROME. Matsuda, H., Satke, Y. and Katsumata, H. (Department of Ophthalmology, Hokkaido University School of Medicine, Sapporo), Jap. J. Ophth. 14:237-246, Oct-Dec., 1970.

The cellular elements of the cornea of a patient with Hurler's syndrome showed vacuoles containing substances apparently secreted through clefts in the cell membrane. These vacuoles are felt to be specific for Hurler's syndrome. (8 figures, 3 tables, 19 references) —Paul A. Hein, Jr.

FALSE OR EXAGGERATED NARROWNESS OF RETINAL ARTERIOLES IN HYPERTENSIVES—COMPARATIVE STUDY OF COLOR AND FLUORESCEIN FUNDUS PICTURE IN HYPERTENSIVES. Matsumoto, K. (Department of Ophthalmology, Surugadai, Nihon University Hospital, Tokyo), Jap. J. Ophth. 14:263-268, Oct.-Dec., 1970.

The irregularity of the retinal arterioles in hypertensives is reduced or eliminated when these arterioles are studied by fluorescein angiography. This is thought to be the result of perivascular retinal cloudiness. (6 figures, 6 tables, 3 references)—Paul A. Hein, Jr.

## INVESTIGATIVE OPHTHALMOLOGY

ULTRASTRUCTURE OF "TUBULAR BODY" IN THE ENDOTHELIAL CELLS OF THE OCULAR BLOOD VESSELS. Matsuda H. and Sugiura, S. (Department of Ophthalmology, Hokkaide University School of Medicine, Sappor, Japan), Invest. Ophth. 9:919-925, Dec., 1970.

Characteristic tubular bodies were detected with great regularity in the endothelial cells of the blood vessels of human eyes, normal and pathologic, as well as in growing vessels in rabbit corneas. These bodies in the mature form are shaped like a cylindrical rod with an internal tubular structure, bounded by a limiting membrane of unit membrane type. It is interesting that they are numerous in some instances of Behcet's disease. (11 figures, 5 references)—Authors' abstract

EXPERIMENTAL MYOPIA IN RABBITS. Tokoro, T. (Department of Ophthalmology, Washington University School of Medicine, 660 S. Euclid, St. Louis, Mo.), Invest. Ophth. 9:926-934, Dec., 1970.

About 1 diopter (D) myopic change was induced experimentally in rabbit eyes by raising the body temperature and increasing the intraocular pressure with a specially designed suction cup. The myopic changes only took place when the body temperature was 41 to 43°C, intraocular pressure was above 40 mm Hg, and topical atropine was given. Eyes subjected to repeated high pressure after the initial experiment exhibited greater changes. It seemed that imbalance between the intraocular pressure and elastic properties of the eye coat produced myopia. (5 figures, 13 references)—Author's abstract

OCULAR RIGIDITY AND DECAY CURVES ANALYZED BY TWO NONLINEAR SYSTEMS. Lyon, C., McEwen, W. K. and Shepherd, M. D. (Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmology, University of California Medical Center, San Francisco, Calif.), Invest. Ophth. 9:935-945, Dec., 1970.

A mathematical approximation technique has been used for the analysis of pressure-volume and decay curves to see which concept of the mechanical properties of the coats of the eye is the more valid: Friedenwald's concept that the outer coats are nonlinear elastic or a recent concept that the outer coats are nonlinear viscoelastic. With such an approach we can analyze equally well by both systems the pressure-volume curves, but not the decay curves. From a single eye two decay curves may be obtained, their positions depending on whether the eye is kept at an elevated pressure

for a long or a short time. These decay curves cannot be analyzed or matched without conceding that the outer coats of the eye are viscoelastic. By means of pressure-volume and decay curves, it is thus possible to obtain quantitative data on the fundamental nonlinear viscoelastic properties of the enucleated human eye. (12 figures, 5 tables, 11 references)—Thomas M. Aaberg

CORTICOSTEROID PROVOCATIVE TESTING. LeBlanc, R. P. Stewart, R. H. and Becker, B. (Department of Ophthalmology, Washington University School of Medicine, St. Louis, Mo.), Invest. Ophth. 9: 946-948, Dec., 1970.

Topical corticosteroid provocative testing for three to eight weeks was carried out on three groups of patients in order to evaluate effects on aqueous dynamics and visual fields. All changes were reversible and no long-term effects were noted. (1 table, 14 references)—Authors' abstract

EFFECTS OF HYDROXYPROPYL METHYLCELLULOSE AND POLYVINYL ALCOHOL ON INTRAOCULAR PENETRATION OF TOPICAL FLUORESCEIN IN MAN. Waltman, S. R. and Patrowicz, T. C. (Department of Ophthalmology, University of Florida, Gainesville, Fla.), Invest. Ophth. 9:966-970, Dec., 1970.

A slit lamp fluorophotometer was used to measure penetration of topical 2% fluorescein, in various vehicles, into human eyes. The technique provides a sensitive method for measuring attained fluorescein concentrations in the anterior segment of the eye. One-half per cent hydroxypropyl methylcellulose significantly increased the penetration of the drug as compared to penetration with 1.4% polyvinyl alcohol or aqueous solutions. Doubling the concentration of fluorescein in the vehicles doubled the attained intraocular concentrations. Very little of the applied drug penetrated into the anterior segment. (2 figures, 4 tables, 11 references)—Authors' abstract

ARGON LASER PHOTOTHERAPY OF PSEUDOMONAS CORNEAL ULCERS. Fromer, C. and L'Esperance, F. (Department of Ophthalmology, Columbia University, New York, N.Y.), Invest. Ophth. 10:1-8, Jan., 1971.

A new technique with the use of argon laser irradiation of Pseudomonas organisms stained with fluorescein-tagged antibody has proved beneficial in the treatment of these particular corneal ulcers in rabbits. Eleven of thirteen ulcers became negative by culture after laser phototherapy. This specific phototherapy introduces a concept that may have significance in future clinical studies. (4 figures, 1 table, 19 references)—Thomas M. Aaberg

ELECTRON MICROSCOPIC STUDIES ON FUCHS' COMBINED DYSTROPHY I. POSTERIOR PORTION OF THE CORNEA. Iwamoto, T. and DeVoe, A. G. (Department of Ophthalmology, Columbia University, 635 W. 165th St. New York, N. Y.), Invest. Ophth. 10:9-28, Jan., 1971.

Seven corneal buttons of typical Fuchs' combined dystrophy were studied with the electron microscope. Descemet's membrane was markedly thickened in six cases and showed various structural alterations. Five different regions could regularly be distinguished in the pathologic Descemet's membrane in all cases. From anterior to posterior they were (1) "anterior banded region" with 1,000 A-banded pattern, (2) "non-banded region," without clear banding (these regions are seen in normal corneas); (3) "posterior banded region" filled with 1,000 A-banded material ("warts" are formed by its partial backward protrusions); (4) "border region" composed of groups of "thin fibrils," "long-spacing bundles" of 1,000 A periodicity with two types of banded pattern, and "basement membrane-like material"; and (5) "fibrillar region" which consists of "basement membrane-like material" and collagen fibrils. (32 figures, 47 references)—Thomas M. Asberg

ELECTRON MICROSCOPIC STUDIES ON FUCHS' COMBINED DYSTROPHY II. ANTERIOR PORTION OF THE CORNEA. Iwamoto, T. and DeVoe, A. G. (Department of Ophthalmology, Columbia University, 635 W. 165th St., New York, N.Y.), Invest. Ophth. 10:29-40, Jan., 1971.

Anterior portions of the central corneas of Fuchs' combined dystrophy were studied with

the electron microscope. The epithelium showed various grades of cellular edema, mostly in the basal layer sometimes coalescing to form subepithelial bullae. Alterations of the subepithelial region paralleled or followed the epithelial changes. Active fibroblasts and collagen fibrils formed large subepithelial masses of connective tissue. Alterations of Bowman's layer and stroma were less marked, although some changes were seen in the stroma as compared with normal controls. All this indicates that the changes in the anterior cornea in Fuchs' dystrophy are secondary to the involvement of the posterior portions. (29 figures, 19 references)—Thomas M. Aaberg

OUTER SEGMENT PRODUCTION AND REMOVAL IN THE DEGENERATION RETINA OF THE DYSTROPHIC RAT. Herron, Jr., W. L., Riegel, B. W. and Rubin, M. L. (Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, Fla.), Invest. Ophth. 10:54-63, Jan., 1971.

The pigment epithelium of the dystrophic rat, as studied by autoradiography, shows an inability to remove its rod outer segment material. By 36 days of age, photoreceptor outer segment production in the dystrophic rat gradually ceases, although uptake of amino acids by the inner segment still appears normal. The first outer segment material which the developing dystrophic rat produces is still adjacent to the pigment epithelium 120 days later. Subsequently produced outer segment material is removed first apparently, suggesting that the removal of this material may be through the inner retina. (5 figures, 2 tables, 4 references) —Thomas M. Aaberg

ELECTRON MICROSCOPIC STUDY OF HEREDITARY CORNEAL EDEMA. Kanai, A., Waltman, S., Polack, F. M. and Kaufman, H. E. (Department of Ophthalmology, College of Medicine, University of Florida and the Veterans Administration Hospital, Gainesville, Fla.), Invest. Ophth. 10: 89-99, Feb., 1971.

Hereditary corneal edema, a previously undescribed corneal dystrophy thought to be transmitted as a dominant trait, was present in five family members. Electron microscopic studies of a corneal button from one member who had penetrating keratoplasty showed absence of the epithelial basement membrane, large fibril-free "lakes" in the middle and posterior stroma, irregular undulating Descemet's layer and an abnormal 2 to 3 cell layer replacing the endothelium. (14 figures, 12 references—Thomas M. Aaberg

EXPERIMENTAL REHYDRATION OF CRYOPRESERVED CORNEAL TISSUE. Edelhauser, H. F., Van Horn, D. L., Gallun, A. B. and Schultz, R. O. (Departments of Physiology and Ophthalmology, Medical College of Wisconsin), Invest. Ophth. 10:100-107, Feb., 1971.

Changes in total water and electrolyte content were measured in corneas following cryopreservation and following experimental rehydration of the cryopreserved-thawed tissue in an albumin-NaCl solution, Kinsey medium, or in vivo in aqueous humor. During the cryopreservation procedure the corneal tissue becomes dehydrated and loses intracellular potassium and sodium. Experimental rehydration of the cryopreserved tissue in Kinsey medium restores the Na+ and water content to control values, but corneal K+ remains decreased. Corneas rehydrated in albumin-NaCl regained only the normal water content; whereas, corneas rehydrated in vivo in aqueous humor regained the normal water content and sodium concentration over a two-hour period, while corneal potassium showed a slight increase throughout the two-hour period. (5 figures, 4 tables, 13 references)—Authors' abstract

CORNEAL EXPOSURE. SODIUM CONCENTRATION IN AQUEOUS AND LENS CHANGES. Bronson, L. J. and Lazar, M. (Department of Ophthalmology, Mount Sinai School of Medicine, City University of New York, New York, N.Y.), Invest. Ophth. 10:144-146, Feb., 1971.

In this experiment, changes in the colligative properties of hamster aqueous were measured as related to corneal exposure and the development of lens opacity. A rise of sodium concentration of aqueous was found to parallel the appearance and progression of lens opacity, indicating the sodium exerted on osmotic effect on the lens. This is consistent with the speculated relationship between corneal exposure and reversible cataracts. (1 figure, 7 references)—Thomas M. Aaberg

CATION CHANGES IN THE LENS AND AQUEOUS DURING THE INDUCTION OF ACUTE REVERSIBLE LENS OPACITY IN THE HAMSTER. Peterson, L. H. (John E. Weeks Institute for Advancement of Ophthalmology, University of Oregon Medical School), Invest. Ophth. 10:147-150, Feb., 1971.

The induction of acute reversible lens opacities in the Syrian hamster following corneal exposure and phenylephrine mydriasis is accompanied by an increase in the sodium and potassium concentration and a decrease in the water content of the lens. There is a simultaneous increase in sodium concentration in the aqueous humor. Final analysis of the effect of various drugs on these lens opacities should reveal that the potentiation of cataracts is proportional to the effect on evaporation of the cornea or aqueous production or both. (2 tables, 10 references)—Authors' abstract

## KLINISCHE MONATSBLATTER FÜR AUGENHEILKUNDE

INDICATION FOR IRRADIATION THERAPY IN OPHTHALMOLOGY. (German) Haye, C. and Calle, R. (23 bis., Avenue Niel, Paris 17 e, France), Klin. Mbl. Augenh. 156: 761-770, June, 1970.

Lid epitheliomas, retinoblastomas and radiosensitive tumors of the orbit (lymphoid tumors) should be irradiated after tumor diagnosis through biopsy. Epitheliomas: small, superficial lesions (up to 1.5 cm in diameter and 0.5 cm in thickness) receive contact irradiation (a total of 4800 r cutaneous dose in 10 to 12 sessions). Middle-sized tumors are conventionally irradiated with total doses of 4600 to 6000 r/field over 5 to 6 weeks. Extensive lesions receive 6500 to 8000 r beta-irradiation (betatron) over 6 to 7 weeks. Healing occurs in 75% of these cases. Retinoblastomas: When enucleation reveals optic nerve invasion, beta irradiation is indicated. In smaller tumors (less than 4 prism diopters prominence and less than ⅓ of the fundus involved) chemotherapy in combination with beta-irradiation cures about 80% of the patients. Orbital tumors: Lymphocytic tumors, lymphosarcomas and reticulosarcomas should be treated with 3000 to 5000 r conventional irradiation; the regional lymph nodes with cobalt irradiation. Complications involving the radiosensitive structures of the eye are rare, when all available precautions are strictly observed. (3 figures, 1 reference)—Helmut Buettner

RETINAL ADHESION AFTER CRYOSURGICAL APPLICATION. (German) Lincoff, H., O'Connor, P. and Kreissig, I. (New York, N.Y., 10022/USA, 440 East 57. Street; 53 Bonn, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 156: 771-783, June, 1970.

The strength of the cryosurgical adhesion varies directly with the strength of application (200 to 1850 mg adhesive force). However the adhesive strength of a diathermy lesion does not relate to the strength of application. The range of its adhesive strength is approximately the same after cryopexy. The retinal adhesion due to the thermal damage occurs when Müller cell cytoplasm infiltrates newly formed pigment epithelium or Bruch's membrane. (11 figures, 5 references)—Helmut Buettner

PHOTO-COAGULATION OF RETINAL LESIONS AFTER PERFORATING INJURIES. (German) Ullerich, K. and Kammann, J. (46 Dortmund, Beurhausstrasse 40, Krankenanstalten Augenklinik, West-Germany), Klin. Mbl. Augenh. 156:783-807, June, 1970.

The prognosis of perforating injuries of the eye is especially poor when the vitreous cavity has been opened and the retina has been damaged. The prognosis is adversely affected by the occurrence of a retinal detachment. The detachment usually arises from a retinal break produced by the foreign body or the surgeon when attempting its extraction, traumatically induced vitreous traction or shrinkage of superficial retinal scars. In order to prevent these posttraumatic retinal detachments, 42 out of 372 patients with perforating injuries and involvement of the posterior parts of the eye received photocoagulation treatment of the posterior pole lesions. It is important, to limit photocoagulation to the smallest necessary intensity and area, in order to avoid retinoschisis, retinal breaks or shrinkage of the retinal surface. Forty out of these 42 patients showed, 29 months later, a favorable anatomical and

functional result. (4 figures, 2 tables, 21 references)—Helmut Buettner

COMPUTER APPLICATION IN CLINICAL ELECTRORETINOGRAPHY. (German) Schmidt, B. and Straub, W. (355 Marburg/Lahn, Univ. Augenklinik West-Germany), Klin. Mbl. Augenh. 156:808-820, June, 1970.

Small ERG potentials, for example in cases of retinitis pigmentosa or when lid margin electrodes have to be used (uncooperative children, corneal diseases) can not be recorded with the regular set-up. In such cases, by using a computer, which averages the data of repeated recordings, a diagnostic ERG can be obtained. The computer ERGs of normal children and adults with special regard to the range of the a- and b-wave amplitudes and their latencies are reported. The authors present the ERG data in cases of RLF, vitelliform cyst of the macula, microphthalmus with congenital cataract, retinal degeneration, corneal ulcer and symblepheron. (7 figures, 6 tables, 13 references)—Helmut Buettner

DISTURBANCES OF VISUAL SENSATIONS IN BI-TEMPORAL HEMIANOPSIA AND DISPLACEMENT OF THE VISUAL AXES. (German) Nachtigäller, H. and Hoyt, W. F. (46 Dortmund, Beurhausstr. 40 Augenklinik; U. C. Medical Center, Moffit, Parnassus San Francisco, Calif. 94122), Klin. Mbl. Augenh. 156: 821-836, June, 1970.

The authors describe some sensory phenomena in bitemporal hemianopsia which are explained by the existence of a cuneiform field behind the point of fixation from which no picture objects can be recognized. These phenomena become manifest through a displacement of the visual axes towards each other. The two intact nasal halves of the visual field which in the binocular visual act in orthophoria meet in the vertical line running through the point of fixation, are separated, partially placed above each other or displaced vertically at the deviation of the visual axes into convergence or in vertical direction. Thus surprising sensory phenomena arise which are discussed in detail (extinction of objects, middle field diplopia, vertical shifts of images, shortening and prolongation effects). (17 figures, 4 references)—Authors' abstract

OCULAR NEUROMYOTONY. (German) Ricker, K. and Mertens, H. G. (87 Würzburg, Neurol. Univ. Klinik, West-Germany), Klin. Mbl. Augenh. 156:837-842, June, 1970.

Hypersensitivity and spontaneous potential formation due to pathologic changes in motor nerve membranes are called "parabiosis." This condition is well known in skeletal muscles, but has not yet been described as occurring in ocular muscles. A 42-year-old female complained about sudden and repeated occurrence of a short-lasting convergent strabismus of the left eye with diplopia. EMG examination revealed a pathologic activity of the peripheral neurogenic type, causing a spasm of the internal rectus muscle. Since other etiological factors (brain stem lesion, basal aneurysm, thyroid problem, orbital myositis) could be excluded and a membrane stabilizing medication (carbamazepine) made the disturbance disappear immediately, the authors call this a case of ocular neuromyotony. (3 figures, 6 references)—Helmut Buettner

CONCENTRATION DYNAMICS OF TETRACYCLINE IN THE HUMAN AQUEOUS HUMOR AFTER ORAL ADMINISTRATION. (German) Knothe, H., Moog, E., Vogel, F. and Fabricius, K. (6 Frankfurt a. M., Paul-Ehrlich-Str. 40, Hygiene Inst. d. Univ. and 23 Kiel, Hehewischstr. 2 Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 156: 843-850, June, 1970.

One hundred and fifty-six patients with cataract received, at different times before surgery, one or several oral doses of 500 mg tetracycline. At the start of the operation, both serum and aqueous humor were withdrawn and their tetracycline content determined in the agar-plate diffusion test. In comparison to the values reported in the literature, the elimination of tetracycline from the serum is somewhat retarded, which might be due to the high average age of our patients (72 years). After equalization by diffusion the aqueous humor level amounts to only 16 to 17% of the serum level or, if put in relation to the non-protein-bound portion of tetracycline in the serum, to 24% ± 2.5 of the plasma water level. After three doses of 500 mg tetracycline at intervals of eight hours, levels of up to 1.2 μg/ml are reached in the aqueous humor. In the case of an intraocular inflammation with reduced blood-aqueous-barrier, effective aqueous humor concentrations of between 3 and 5 μg/ml

can be expected because of the slight affinity of tetracycline to the serum protein when given in the aforementioned dosage. In the treatment of intraocular bacterial infections tetracycline itself should be given preference instead of its derivatives pyrrolidino-methyl-tetracycline and demethylchlortetracycline. (2 figures, 2 tables, 24 references)—Authors' abstract

COLOBOMA OF IRIS AND CHOROID IN XYY-SYNDROME. (German) Schwinger, E. and Wiebusch, D. (53 Bonn, Stiftsplatz 12, Univ. Inst. f. Gerichtl. Med.; 53 Bonn-Venusberg, Univ. Augenkl. Bonn, West-Germany), Klin. Mbl. Augenh. 156:873-877, June, 1970.

Ocular malformations can be related to chromosomal aberrations such as a luxated lens in 47 XYY-syndrome. The authors report another ocular defect, which might have been caused by this chromosomal aberration. Cytogenetic investigations in a 19-year-old man with a large coloboma of the iris and the choroid revealed a 47 XYY-karyotype. The patient also had above average height, psychic and social problems (prison inmate) and gonadal atrophy, features known to occur in 47 XYY chromosome aberrations. (2 figures, 23 references)—Helmut Buettner

## NEUROLOGY

EPISODIC BLINDNESS AS A LATE EFFECT OF HEAD TRAUMA. Kooi, K. A. (Electro-encephalography Laboratory, University of Michigan Medical Center, Ann Arbor), Neurology 20:569-573, June, 1970.

Three patients who had episodic blindness as a major complaint some years following head trauma were shown to have significant deviations in the responsivity of the visual system to series of photic stimuli. It was postulated the symptom represented an inhibitory visual seizure. (3 figures, 10 references)—Joel G. Sacks

INTERNUCLEAR OPHTHALMOPLEGIA AS AN EARLY SIGN OF BRAINSTEM TUMORS. Cogan, D. G. and Wray, S. H. (Howe Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston), Neurology 20:629-633, July, 1970.

Six patients with tumors of the brainstem are described in whom internuclear ophthalmoplegia was a prominent feature. This syndrome is an unusual feature of tumors and may lead to confusion with demyelinative disease. (2 figures)—Authors' abstract

## NEW ENGLAND JOURNAL OF MEDICINE

TRANSIENT CORTICAL BLINDNESS: STILL AN "OVERLOOKED" SYNDROME? Carmola, J. R. and Harris, B. S. (Dartmouth Affiliated Hospitals), New England J. Med. 282:1325, June, 1970.

Three cases of transient cortical blindness following head injury are described out of only 267 neurosurgical patients seen in an emergency room. The paucity of clinical reports and further investigation of this entity suggest that this is an "overlooked" syndrome. (4 references)—Joel G. Sacks

TAY-SACHS DISEASE: DETECTION OF HETEROZYGOTES AND HOMOZYGOTES BY SERUM HEXOSAMINIDASE ASSAY. O'Brien, J. S., Okada, S., Chen, A. and Fillerup, D. L. (Department of Neurosciences, School of Medicine, University of California, San Diego), New England J. Med. 283:15-20, July, 1970.

A fluorometric method showed the activity of hexosaminidase A to be markedly deficient in serum specimens from nine patients with Tay-Sachs disease. Parents (obligate heterozygotes) of children with Tay-Sachs disease had levels of hexosaminidase A that were intermediate between those found in affected children and those in control groups. No overlap was found between values for this enzyme in serums from heterozygotes, healthy controls and homozygotes. (6 figures, 2 tables, 5 references)—Joel G. Sacks

## OPHTHALMIC RESEARCH

OCULAR SIDE-EFFECTS OF LONG-TERM IMMUNOSUPPRESSIVE THERAPY IN RECIPIENTS OF CADAVER KIDNEY TRANSPLANTS.

Zaruba, R. K. and Scheitlin, W. (University of Zurich, Kantonsspital Zurich), Ophth. Res. 1:21-30, 1970.

This is a report of an ophthalmologic survey of 28 bilaterally nephrectomized patients with a unilateral cadaver kidney transplant, kept under a continuous immunosuppressive therapy for up to 48 months. Two types of cataracts were delineated: anterior subepithelial and posterior subcapsular cataracts, brought about by the corticosteroid treatment, and "Glaukomflecken"—like, subepithelial spots, possibly induced by a transient failure of the kidney transplant. (4 figures, 5 tables, 15 references)—Authors' abstract

THE RELATIONSHIP BETWEEN ERG AND VER. van Lith, G. H. and Henkes, H. E. (Eye Clinic, Medical Faculty, Rotterdam), Ophth. Res. 1:40-47, 1970.

From a comparison between local cone-ERG and VERs, elicited with disc and ring stimuli, it appeared, that the local cone ERG is highest in the macular region, because it is only dependent on the number of cones stimulated. The VER, too, is mainly determined by the central retinal area. Apart from the high cone density in the macular region this is also due to the fact, that the contribution of the central cones is higher than that of the peripheral cones. This is caused partly through the convergence of the extra-foveal cones in the ganglion cells, partly through the localization of the retinal projection in the area striata. (4 figures, 17 references)—Authors' abstract

ULTRASTRUCTURAL CHANGES IN THE RAT PHOTORECEPTOR INNER SEGMENT DURING EXPERIMENTAL CHLOROQUINE RETINOPATHY. Solze, D. A. and McConnel, D. G. (Ohio State University, Columbus, Ohio), Ophth. Res. 1:140-148, 1970.

Hooded rats were given chloroquine phosphate (Aralen) over an eight month period during which regular indirect ophthalmoscopic examinations were performed. When retinal or anterior ocular changes were observed in poisoned rats, retinas were prepared for electron microscopy. Significant ultrastructural changes were localized in the inner segments of the receptor cells, where mitochondrial swelling, disappearance of the ciliary process and disorganization of the endoplasmic reticulum were observed. Observations were consistent with previous clinical, light microscopic and electroretinographic findings. (3 figures, 1 table, 27 references)—Authors' abstract

RESPONSE OF THE MOUSE LENS TO HIGH CONCENTRATIONS OF GLUCOSE OR GALACTOSE. Kuck, Jr., J. F. R. (Emory University, Atlanta, Ga.), Ophth. Res. 1:166-174, 1970.

In vitro studies show that the mouse lens exposed to elevated concentrations of glucose or galactose does not develop the changes which affect the rat lens under similar conditions. The young mouse lens (CFW strain) is resistant to the cataractogenic effect of a galactose diet or alloxan diabetes. This species difference appears to reside in the lens itself since both sugars can accumulate in the mouse lens to reach levels comparable to those found in the rat lens exhibiting significant changes. (9 tables, 12 references)—Authors' abstract

THE EFFECT OF CHANGES IN ARTERIAL BLOOD PRESSURE ON THE RATE OF AQUEOUS HUMOUR FORMATION IN A PRIMATE. Bill, A. (Institute of Pharmacology, Uppsala, Sweden), Ophth. Res. 1:193-200, 1970.

The rate of aqueous humour formation in vervet monkeys was determined with a dilution method during stepwise reductions in mean arterial blood pressure produced by bleeding the animals. The mean rate of aqueous humour formation at a mean arterial blood pressure of 119 ± 7 mm Hg was 2.64 ± 0.22$\mu$ 1/min (n = 11). Bleeding the animals to a pressure of 70 to 90 mm Hg had little effect on the rate of aqueous formation. Further reductions in mean arterial blood pressure usually decreased aqueous formation markedly. Interruption of the sympathetic supply to the eye under study had no appreciable effect on the relationship between rate of aqueous humour formation and mean arterial blood pressure. (3 figures, 20 references)—Author's abstract

STATISTICAL INVESTIGATIONS OF INTRAOCULAR PRESSURE WITH GOLDMANN'S APPLANATION TONOMETER. Bechrakis, E. (University of Bonn, Germany), Ophth. Res. 1:211-219, 1970.

On the basis of 1,235 anamnestically healthy eyes, the author shows that intraocular pressure after transformation is of normal loga-

rithmic distribution with a high degree of probability and is not bimodal, at least not in the pressure range between 6 and 32 mm Hg. For this reason a division into "glaucoma" and "non-glaucoma" solely on the basis of intraocular pressure without additional information is not permissible. (5 figures, 2 tables, 9 references)—Authors' abstract

BILATERAL LACRIMAL GLAND ENLARGEMENT ASSOCIATED WITH A DIFFUSE GAMMA GLOBULIN ELEVATION. Yanoff, M., Nix, R. and Arvan, D. (University of Pennsylvania, Philadelphia), Ophth. Res. 1:245-253, 1970.

A patient with PAS-positive intranuclear plasma cell inclusions in the lacrimal gland is reported. Immunoelectrophoresis showed a diffuse elevation of the IgG and IgA fractions but a normal IgM fraction. No abnormal proteins (M-components) were found. (5 figures, 12 references)—Authors' abstract

## OPHTHALMOLOGICA

THE HYPERPYREXIA SYNDROME AS COMPLICATION AFTER INTRAOCULAR OPERATIONS IN INFANTS. (German) Kintzel, H.-W. and Graupner, K. (Departments of Ophthalmology and Pediatrics, the Academy of Medicine "Carl Gustav Carus," Dresden, Germany), Ophthalmologica 160: 385-390, 1970.

In four infants with congenital cataracts, uncomplicated linear lens-extractions under halothane-nitrous oxide anesthesia were followed by fatal hyperpyrexia. Pre-existing brain damage, related in etiology to the cataracts, is assumed to be a predisposing factor. Hourly temperature readings after the operation and prompt use of antipyretics if the temperature rises 1°C above normal are recommended. (6 references)—Peter C. Kronfeld

GLAUCOMA AND DIABETES. (German) Hauff, D. (Eye Clinics of the Humboldt University in Berlin and of the County Hospital Berlin-Friedrichshain), Ophthalmologica 160:391-397, 1970.

In a series of 962 cases of primary glaucoma the prevalence of diabetes was 13%, that is, considerably higher than in unselected (general) populations with corresponding age distribution. (4 figures, 2 tables, 24 references)—Peter C. Kronfeld

ANTERIOR VITREOUS CHANGES FOLLOWING CATARACT EXTRACTION BY CRYO-SURGERY. Joyce, M. and Sollom, A. W. (The Wolverhampton and Midland Counties Eye Infirmary), Ophthalmologica 160:398-402, 1970.

The authors' material consisted of 100 eyes on which uncomplicated lens extractions by a standardized cryo-technique had been performed during the previous three years. The term anterior hyaloid membrane is used for the interface at which a change in optical density can be seen between aqueous and vitreous. In 70 of the 100 eyes one or more holes were found in the anterior hyaloid membrane; 32 cases had developed localized and 17 cases general spreading of vitreous into the anterior chamber. The vision was demonstrably disturbed only in the cases of general spreading of the vitreous.

The percentage of holes in anterior hyaloid with consequent protrusion of vitreous was much higher than in other reported series where cataracts were extracted by other methods. For this reason the authors consider it possible that we may see increased instances of postoperative complications following cryo-extractions. (5 references)—Peter C. Kronfeld

THE EFFECT OF ANTI-INFLAMMATORY DRUGS, CORTICOSTEROIDS AND TANDEARIL, UPON THE INTRAOCULAR PRESSURE. (French) Younessian, S. and Psilas, K. (University Eye Clinic Geneva, Switzerland), Ophthalmologica 160:403-408, 1970.

In a series of 11 glaucoma suspects one eye was treated with 0.5% prednisolone t.i.d. and the other with a 10% ointment of Tandearil (oxyphenbutazone) b.i.d. During a test period of three weeks the corticosteroid produced statistically significant rises in pressure and drops in outflow facility while the Tandearil-treated eyes showed no significant change in aqueous-dynamics. The latter observation was confirmed in nine eyes with overt primary open-angle glaucoma in which the Tandearil-ointment was added to the pressure-normalizing medication. Cases of uveitis in which ocular

hypertension had developed under the influence of topical corticosteroids, responded very well to topical Tandearil ointment, in terms of pressure as well as in terms of ocular inflammation. (2 tables, 8 references)—Peter C. Kronfeld

DIFFERENTIAL MACULAR ILLUMINATION TESTS. Paul, S. D. and Singh, K. M. (Department of Ophthalmology, Postgraduate Institute of Medical Education and Research, Chandigarh, India), Ophthalmologica 160:409-420, 1970.

The test consists of measurements of the recovery of the visual acuity following a standardized amount of mild macular dazzle. As originally proposed by Baillart, white light was used for illumination of the macula. The authors of the present paper added dazzling and recovery measurements through red and green filters. They now present findings in 124 controls and in 170 cases of macular lesions. In early macular degeneration or early angiospastic maculopathy the response with the red filter is more delayed than that with the green filter; the reverse order is found in late macular degenerations or healed angiospastic maculopathy. The differential macular illumination test allows recognition of macular degeneration when the ophthalmoscopic appearance of the macula is still normal. (8 tables, 5 references)—Peter C. Kronfeld

REGARDING THE TECHNIQUE OF EYE EXAMINATIONS FOR STRABISMUS IN INFANTS AND SMALL CHILDREN. (German) Šeba, J. (The Polyclinic of the County Institute for Community Health, Rychnow and Knežňou, Czechoslovakia), Ophthalmologica 160: 421-429, 1970.

On the basis of extensive experience of eye examinations of newborns and small children the author has extended and refined Brückner's transillumination test which was designed to give answers to the questions: 1) Is strabismus present, and 2) Is there a danger of amblyopia? Between 1962 and 1964 the present author used his modification of the test for the examination of 1592 small children with ages ranging from four months to two and a half years. In 126 of these children the test revealed the presence of strabismus or of refractive conditions likely to lead to amblyopia. In the course of routine pre-school eye examinations the status of the entire population of 1592 children became known again. Of the children in whom the original test had been negative, eight had developed strabismus (between the ages of three to five years) and nine showed a mild degree of amblyopia due to an anisometropia which had not been present or had not been detected at the first examination. The author's method apparently yields the largest number of children at risk. (7 references)—Peter C. Kronfeld

## SCIENCE

TESTING THE VISION OF CATARACT PATIENTS BY MEANS OF LASER-GENERATED INTERFERENCE FRINGES. Green, D. G. (Dept. of Ophthalmology, University of Michigan, Ann Arbor), Science 168:1240-1242, 1970.

The fineness of the laser-generated interference fringe that the cataract patient can detect gives an indication of the potential for postoperative improvement in vision. (1 figure, 5 references)—Joel G. Sacks

CATARACTS PRODUCED IN RATS BY YOGURT. Richter, C. P. and Duke, J. R. (Psychobiology Laboratory and Wilmer Eye Clinic, Johns Hopkins Hospital, Baltimore, Md.), Science 168:1372-1374, 1970.

Rats kept on an exclusive diet of yogurt avidly ate the yogurt, grew at a normal rate, were normally active, mated, conceived, and gave birth to normal, healthy litters. However, all of the rats developed cataracts. The cataracts appear to be the same as those produced by diets with a high content of galactose. (3 figures, 9 references)—Joel G. Sacks

## SOUTHERN MEDICAL JOURNAL

MANAGEMENT OF OCULAR ADNEXAL AND MOTILITY PROBLEMS ASSOCIATED WITH MIDFACIAL FRACTURES. McCord, Jr., C. D. (Department of Ophthalmology, Emory University School of Medicine, Atlanta, Ga.), Southern Med. J. 63:842-848, July, 1970.

The clinical course of 41 patients who suffered consecutive fractures to the mid-facial area is reviewed. Double vision is the most

# NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
*700 North Michigan Avenue, Chicago, Illinois 60611*

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### IMPLANT CLUB TO MEET IN BUDAPEST

The Second meeting of the Intra-Ocular Implant Club will be held in Budapest, at the conclusion of the European Ophthalmological Congress, on April 22, 1972. The morning session will be devoted to intracameral lens implants and the afternoon to intracorneal prostheses. Short opening papers will be read by members of the club. Any ophthalmologist who wishes to attend will be welcome. Inquiries should be addressed to Mr. Peter Choyce, F.R.C.S., Secretary, Intra-Ocular Implant Club, 45 Wimpole Street, London, W1M 7 DG, England.

### PEDIATRIC COURSE: AMERICAN UNIVERSITY OF BEIRUT

The department of ophthalmology of the American University medical center, Beirut, Lebanon, is offering a course on pediatric ophthalmology December 3-4, 1971. Guest speakers will be Jules François and Gunter K. von Noorden.

Additional information may be obtained from Camille S. Matta, M.D., Chairman, Department of Ophthalmology, School of Medicine, American University, Beirut, Lebanon.

### SYMPOSIUM: PATHOLOGIC EFFECTS OF LIGHT ON THE RETINA

On September 19, 1971, a joint meeting of the Association for Research in Vision and Ophthalmology and the American Academy of Ophthalmology and Otolaryngology will be held in Las Vegas, Nevada, convention city. The participants and their topics are as follows:

Introduction, Lorenz E. Zimmerman (Washington, D.C.), moderator; Solar retinopathy in man: Clinical features, course, and recovery: Robert Penner, (Chula Vista, California); Photic maculopathy in rhesus monkeys: Clinical features, course, and recovery: Mark D. M. Ts'o (Washington, D.C.); Foveomacular retinitis, an important problem in military medicine: Clinical features and course: Bernard R. Blais (San Diego, California); Foveomacular retinitis: Evidence that sun gazing is causative: Budd Appleton (Washington, D.C.); Effects of prolonged exposure of rabbit retina to low intensity light: Theodore Lawwill (Louisville, Kentucky); Damage to primate retina produced by low intensity light: Toichiro Kuwabara (Boston, Massachusetts); Relationship of vitamin A deficiency to damaging effects of low intensity light: Werner K. Noell (Buffalo, New York); Experimental and therapeutic aspects of photic damage to retina: Eliot L. Berson (Boston, Massachusetts); Summary and suggestions for further research, clinical and experimental: Frank W. Newell (Chicago, Illinois).

### ATLANTIC SECTION: ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY

The Atlantic section of the Association for Research in Vision and Ophthalmology will hold their 1971 meeting at the Fontainebleau Hotel, Miami Beach, Florida, November 1-3, 1971.

Abstracts of papers are to be submitted by September 1, 1971, to Douglas R. Anderson, M.D., Bascom Palmer Eye Institute, 1638 N.W. 10th Avenue, Miami, Florida 33152. Advance registration is requested.

### OFFICERS ELECTED: AMERICAN OPHTHALMOLOGICAL SOCIETY

At the recent meeting of the American Ophthalmological Society held at the Homestead, Hot Springs, Virginia, May 24-26, 1971, the following officers were elected: President, Trygve Gundersen; Vice-President, Arthur G. DeVoe; Secretary-Treasurer, Samuel D. McPherson, Jr.; Editor of Transactions, Clement McCulloch; Council, William F Hughes, Jr.

### MEDICAL ASSISTANCE PROGRAM

The Medical assistance program (MAP) of Wheaton, Illinois, provides medical and surgical supplies to many hundreds of mission hospitals in more than 80 developing nations of the world. Close to 100 pharmaceutical and surgical supply firms donate their products for overseas use. They have shipped medical supplies worth more than $80 million to about 1000 medical missionaries. Those who are interested in donating good used instruments and surgical equipment may write to MAP, Box 50, Wheaton, Illinois 60187, for further details. Would-be donors in the Chicago area may call Larry Dixon at 653-6010.

### SOFT LENS COURSE: UNIVERSITY OF FLORIDA

A practical course on soft contact lenses, sponsored by University of Florida, will be held January 26-29, 1972, immediately preceding the Florida Midwinter Seminar.

The course is designed to provide practical instruction in the selection, fitting, and use of all types of soft contact lenses. It will consist of lectures, round table discussions, demonstrations and workshops on fitting techniques. Faculty will in-

clude: J. Aquavella, J. Baldone, C. Black, V. Chiquiar Arias, G. Feldman, M. Friedberg, A. Gasset, J. Hartstein, H. Kaufman, M. Poster, W. Sampson, M. Uotila, and K. Whitman.

Registration fee is $100 for the seminar and $300 for the seminar and workshop. Attendance will be limited and the deadline for applications is December 1, 1971. For application forms and additional information please write to Antonio R. Gasset, M.D., Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, Florida 32601.

### Two meetings: University of Iowa

The ocular microbiology and immunology group of the department of ophthalmology will meet on September 17, 1971, at the university.

An international symposium on ocular inflammatory disease will be held in Iowa City on November 3-4, 1971.

Further information in regard to either meeting may be obtained from Bruce Golden, M.D., University Hospitals, Department of Ophthalmology, University of Iowa, Iowa City, Iowa 52240.

### Postgraduate course: State University of New York

The department of ophthalmology of the State University of New York Upstate Medical Center in Syracuse will present its 22nd annual postgraduate course in ophthalmology at the Hotel Syracuse, December 3-4, 1971. Guest speakers will be Joseph S. Haas, of Chicago, Marshall M. Parks, of Washington, D.C., and David Paton, of Houston, Texas.

The fee is $35. Enrollment is limited to 90 persons. For further information, contact James L. McGraw, M.D., State University of New York Upstate Medical Center, 750 East Adams Street, Syracuse, New York 13210.

### Postgraduate conference: Estelle Doheny foundation

The Estelle Doheny Eye Foundation sponsors its annual postgraduate conference in Los Angeles, California, on Monday and Tuesday, October 18 and 19, 1971. The principal speakers will be Ramon Castroviejo and Frank W. Newell.

## Personals

### George T. Brooks

Biologist George T. Brooks has been appointed Associate Director for Extramural Programs of the National Eye Institute (NEI) by Institute Director, Carl Kupfer.

Dr. Brooks was formerly Deputy Director of the Division of Research Grants, National Institute of Health. In his new position, he directs the scientific and administrative management of NEI's research and training grants programs. He will also be responsible for conducting a continuous review of Extramural Program content and will serve as a principal advisor to the NEI Director in planning and administering Institute programs, policies, and operating procedures.

Born in Okmulgee, Oklahoma, Dr. Brooks did undergraduate and graduate work at the University of Kansas. After receiving his Ph.D. degree in entomology in 1949, he became associate professor of biology at Southern University in 1949, and in 1951 was appointed acting head of the biology department. The next year, Dr. Brooks joined the International Cooperation Administration (forerunner of the Agency for International Development) as a research specialist in entomology, and was assigned to advise the Government of Nepal in establishing a plant protection service and malarial control program.

Beginning a series of assignments with the Department of Agriculture's Regional Insect Control Project in 1957, Dr. Brooks served in Pakistan, Lebanon, and Iran, assisting and advising the governments of the Middle East, North and East Africa, and South Asian countries in the control of locusts and other insect pests, and aided in the administration of U.S. technical assistance programs related to these efforts. As part of these activities, he served as the chief consultant for organizing the first Pan Africa seminar on insect control services.

Dr. Brooks came to NIH in 1962 as a Grants Associate. He was appointed Training Consultant to the National Institute of Child Health and Human Development, NIH, in 1963, and in 1965 became Director of the Hematology Grants Program within the National Institute of Arthritis and Metabolic Diseases.

In 1966, Dr. Brooks became Deputy Chief of NIH's Latin American Office and was appointed Chief of the office in 1968. He became Deputy Director of the NIH Division of Research Grants in 1969.

For achievement in the field of biology, Dr. Brooks received the Phi Sigma award of the University of Kansas in 1947. He was nominated in 1954 for the Arthur Fleming Award to honor outstanding young men in the Federal Government.

Dr. Brooks lives in Washington, D.C., is married, and has two children.

### Jin Kinoshita

Jin H. Kinoshita, Ph.D., has been promoted to tenure status as professor of biochemical ophthalmology at Harvard Medical School.

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2. Lacrimal Symposium
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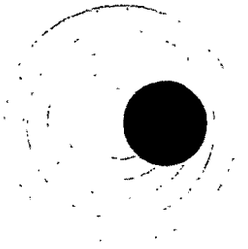
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Registration fee will be $100 for the seminar or $300 for the seminar and workshop. Attendance will be limited and the deadline for applications is December 1, 1971. For application forms and additional information please write:

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Department of Ophthalmology
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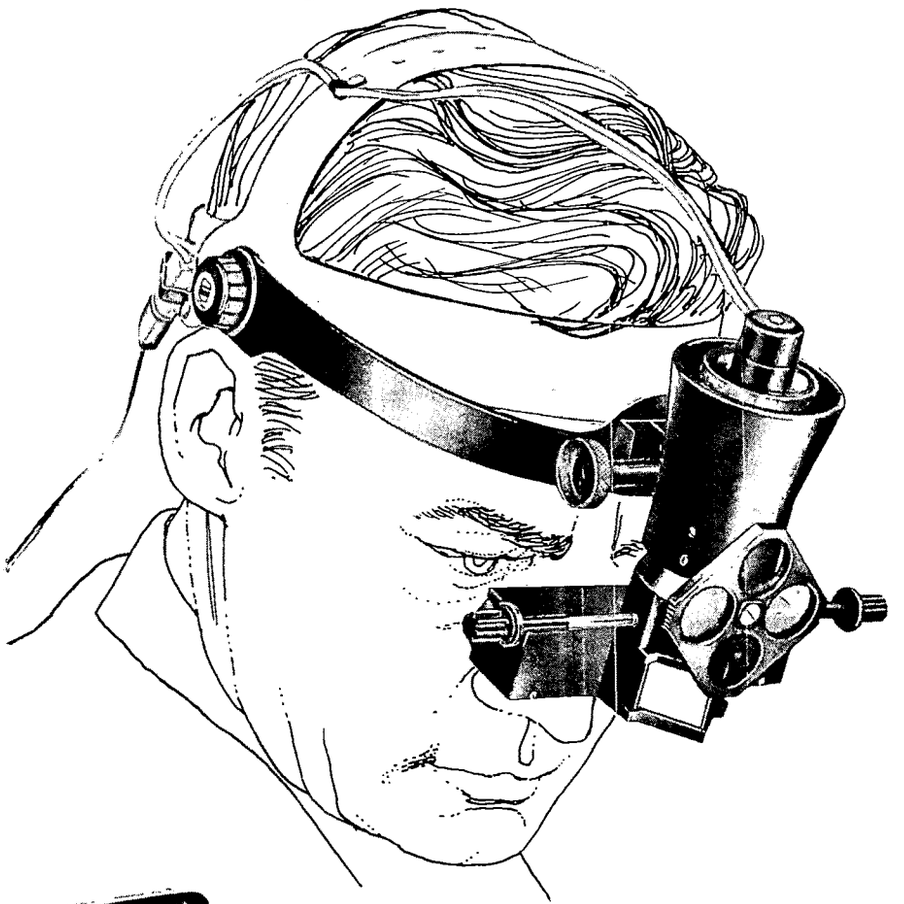
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Further information may be obtained by writing to Robert E. Levine, M.D. or T. Rodman Wood, M.D., Program Chairmen, Estelle Doheny Eye Foundation, 272 South Lake Street, Los Angeles, California, 90057.

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1. Mishima, S. and D. M. Maurice, The Effect of Normal Evaporation on the Eye, Exp. Eye Res., *1*:46, 1961.
2. Bahr, Gunnar, Measurement of the Effect of Solutions of Different Osmotic Pressure on the Thickness of the Living Cornea, Trans. of Ophthal. Soc. U.K., *68*:515, 1949.

# REVISTA DE LA SOCIEDAD COLOMBIANA DE OFTALMOLOGIA

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## Supplemento

En esta sección se publicaran algunos de los trabajos presentados en el VII Congreso ad-interin de la Asociación Panamericana de Oftalmología, reunido en Bogotá del 31 de enero al 5 de febrero de 1971.

Las publicaciones se haran en 4 números consecutivos de la Revista, distribuyéndose los temas en la siguiente forma:

Número 1:
PATOLOGIA DE LA RETINA.

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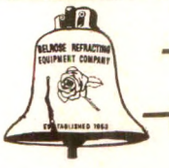
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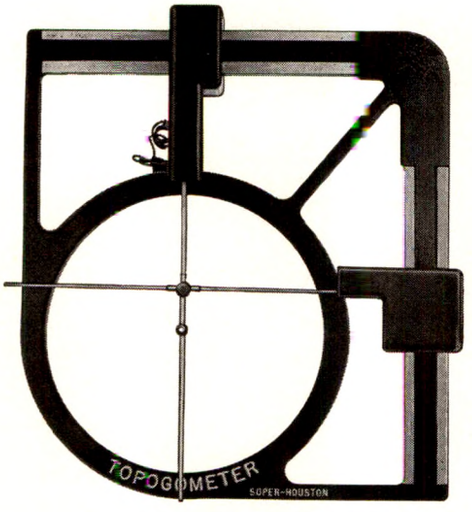
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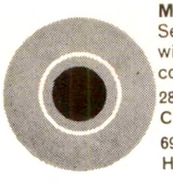
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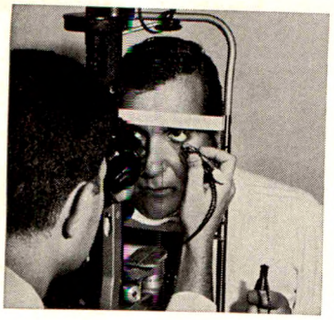
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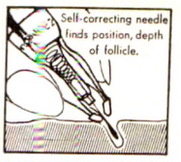
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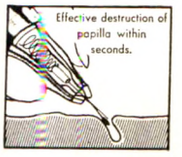
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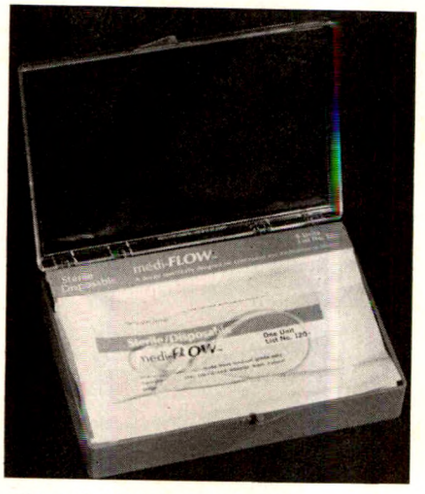
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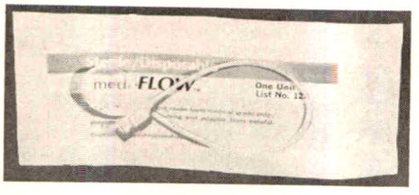
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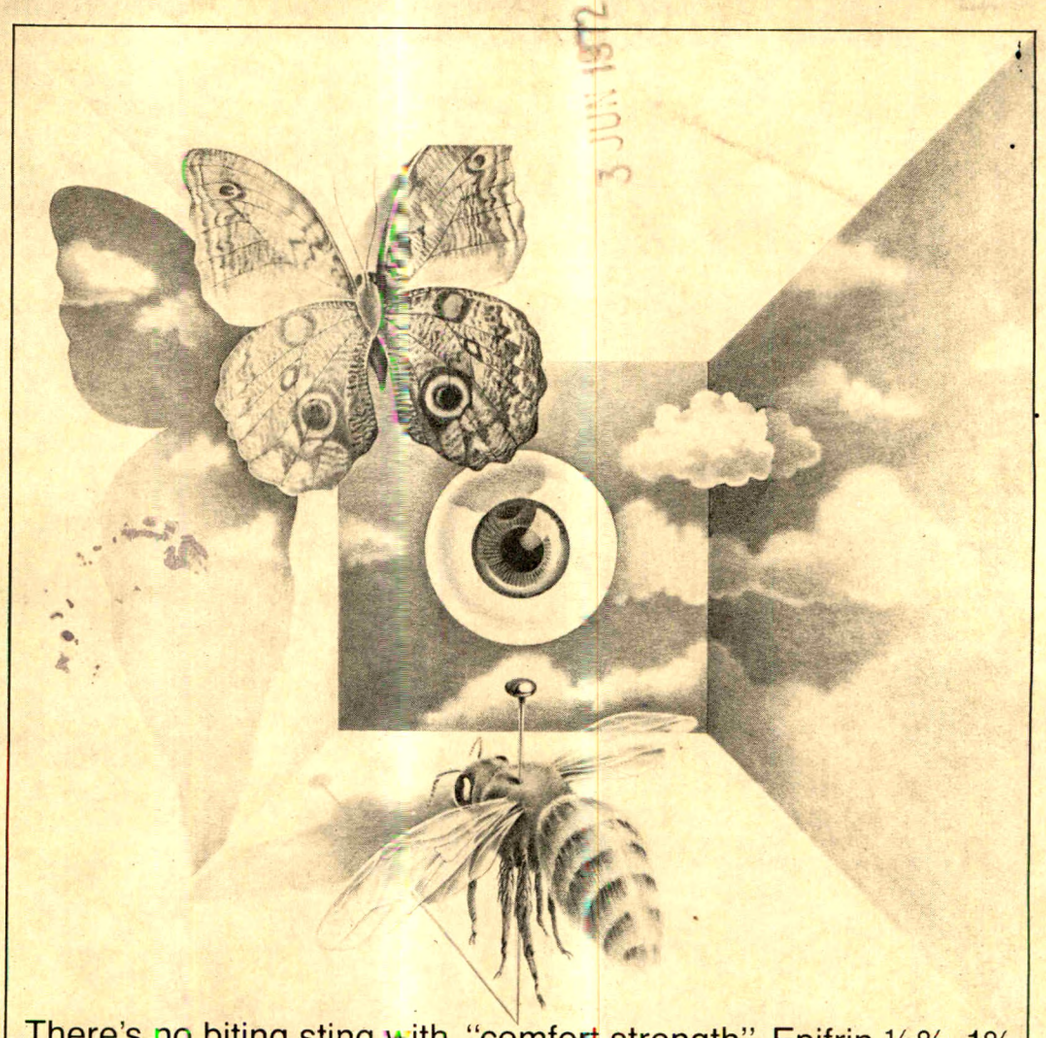

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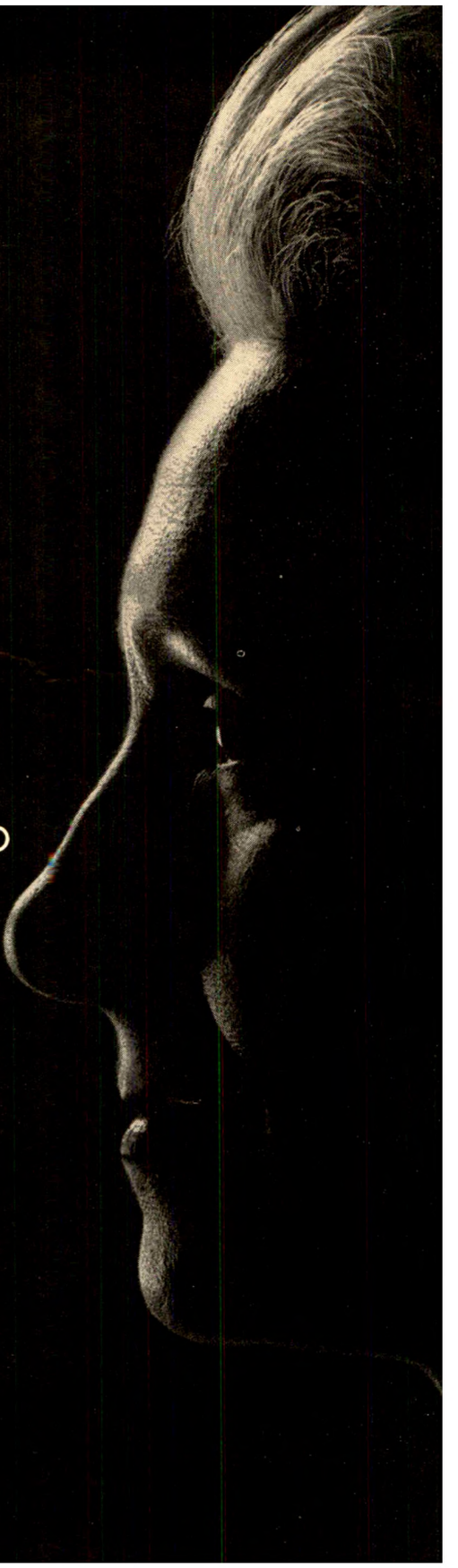
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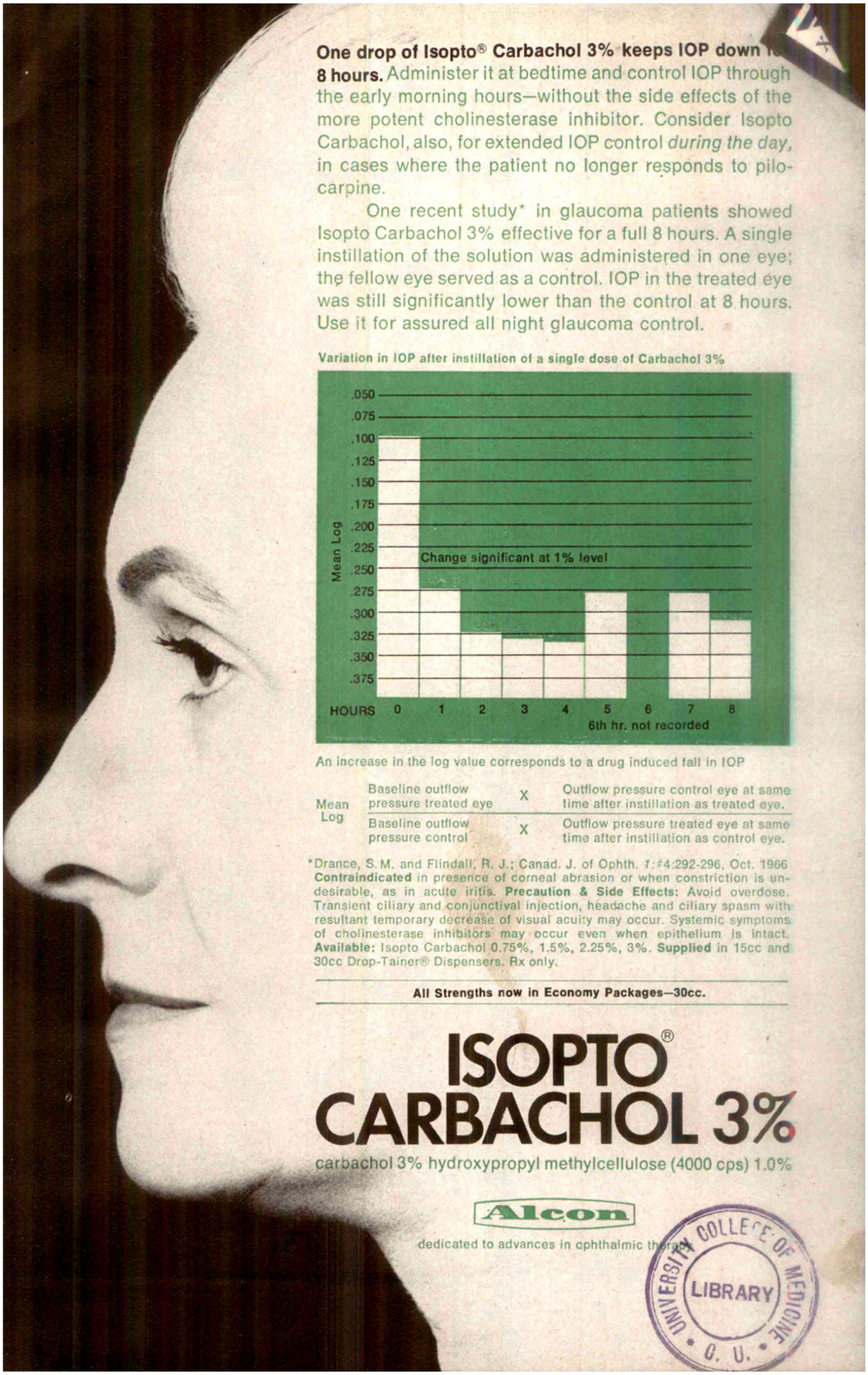
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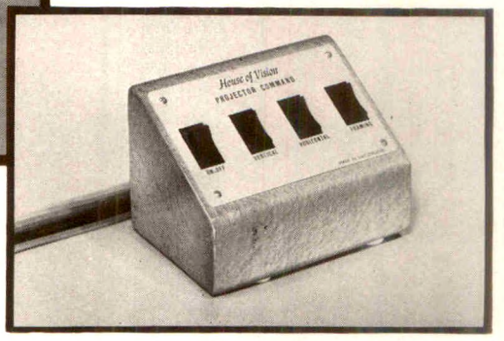
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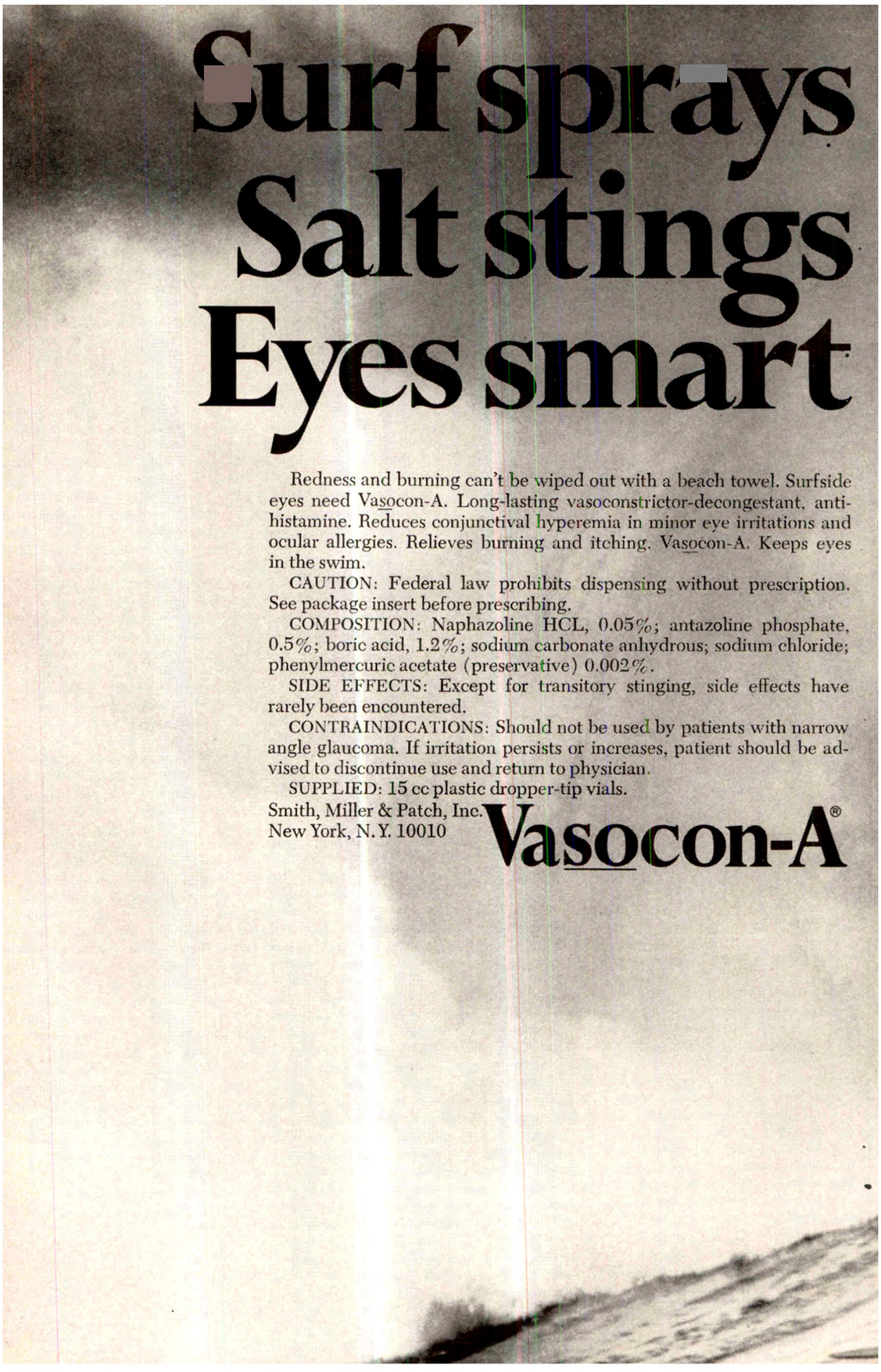
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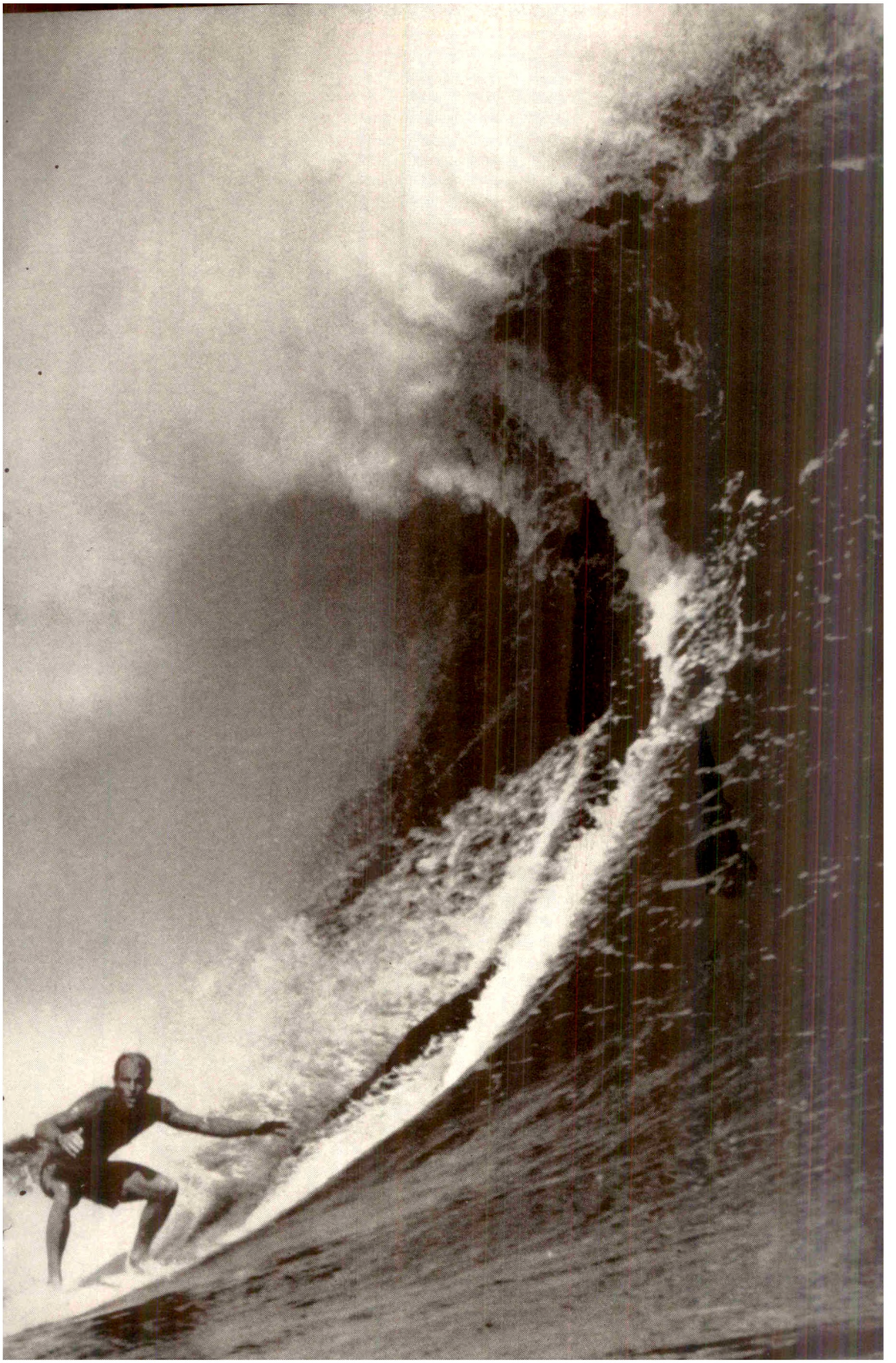
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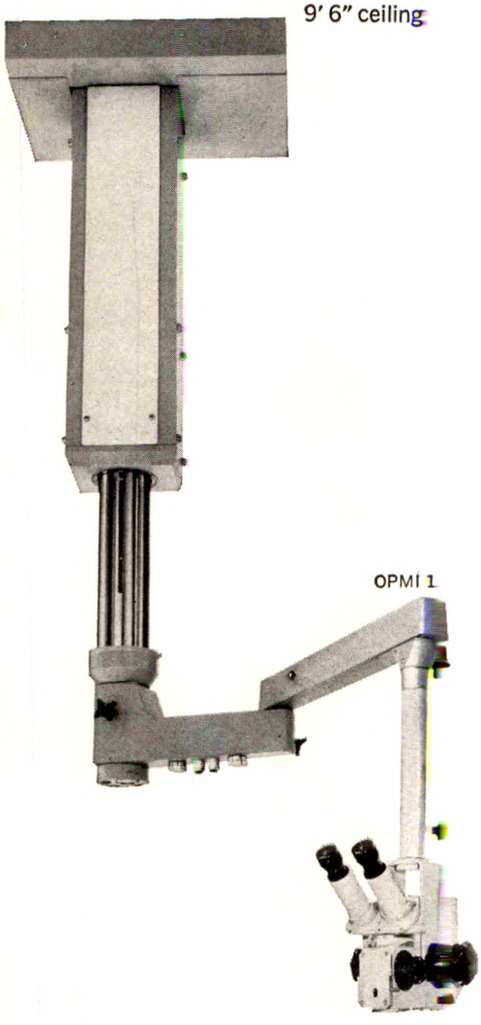
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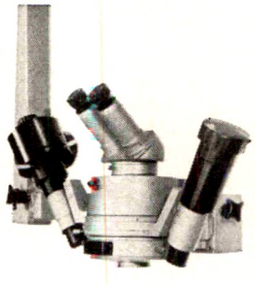
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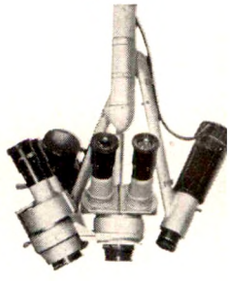
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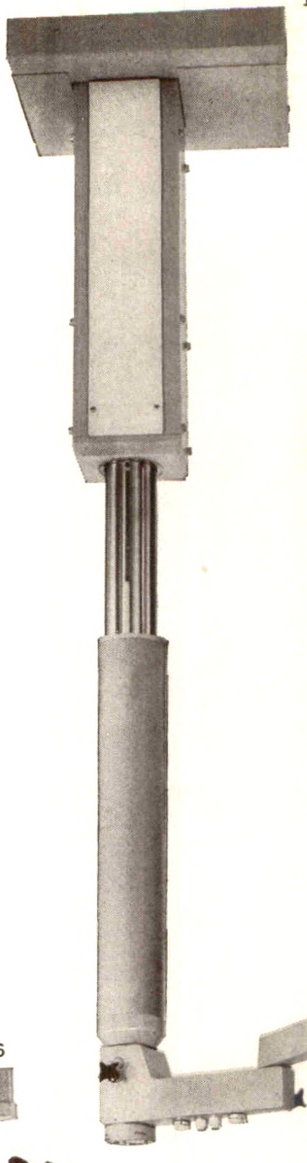
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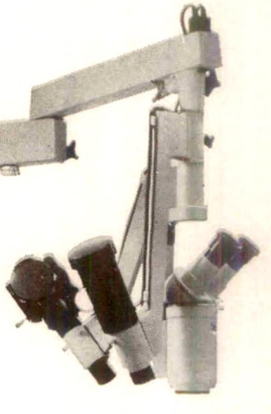
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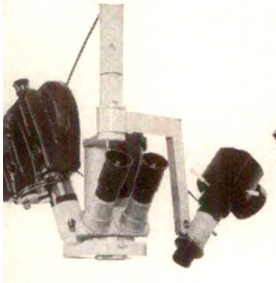
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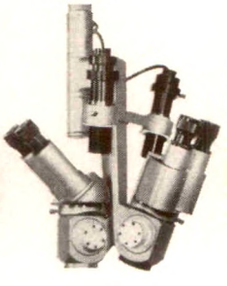
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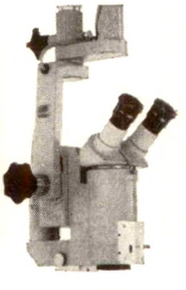
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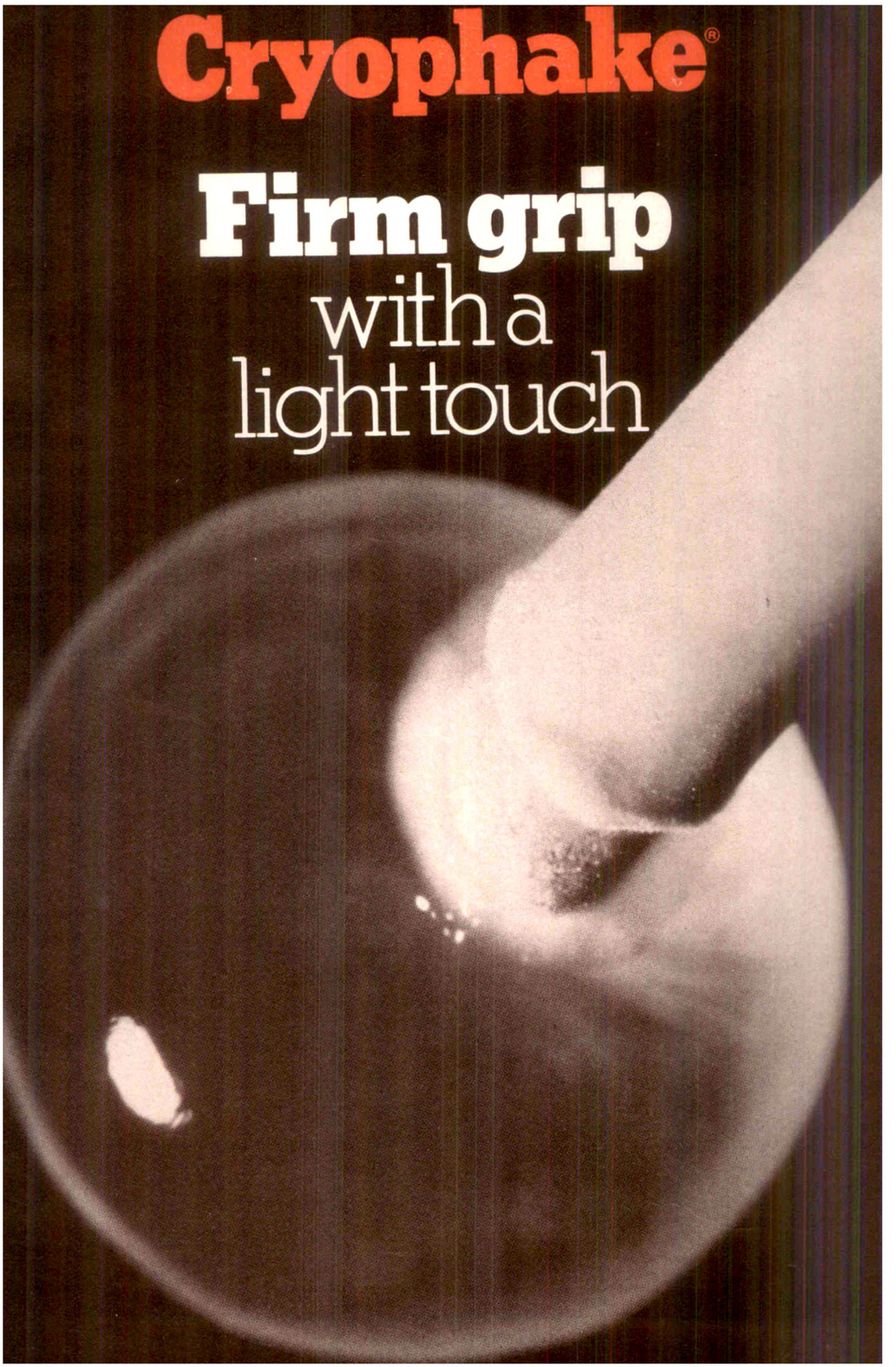
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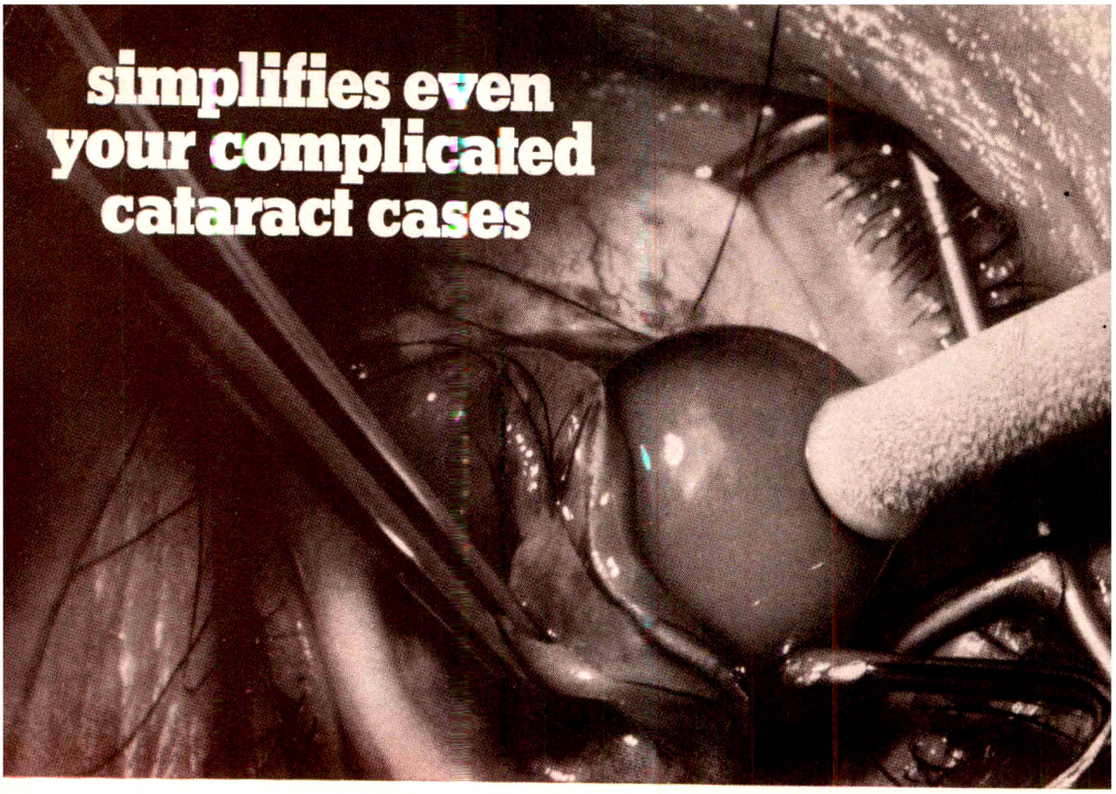
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**1.** Reynolds, A. M., Jr. and King, J. H. Jr.: Evaluation of a new Model Cryoextractor, E.E.N.T. Monthly. *48*:50-51 (Dec.) 1969. **2.** Haik, G. M., Ellis, G. S. and Pollard, J. B.: Selective Cryoextraction of the Cataractous Lens, Amer. J. Ophthal. *61*: 484-490 (March) 1966. **3.** Mattis, R. D., Brady, H. R., and Sugana, T.: Disposable Cryophake—Clinical Evaluation, Arch. Ophthal. *74*:787-791 (Dec.) 1965. **4.** Bellows, J. G.: The Mechanical Superiority and Advantages of Cryoextraction, Amer. J. Ophthal. *61*:1003-1009 (May) Part II, 1966. **5.** Cole, O. W. and Dunnigan, W. J.: Enzymatic Zonulolysis and Cryoextraction of Cataracts, Int. Surg. *50*:3 (Sept.) 1968.

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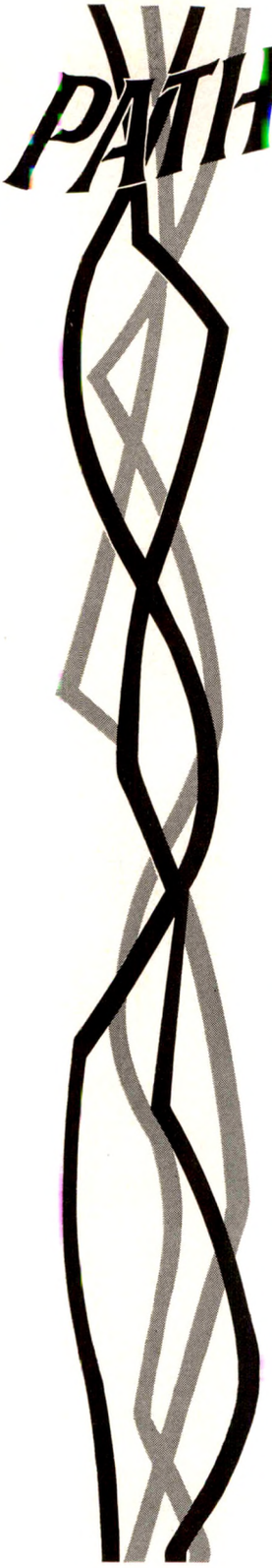
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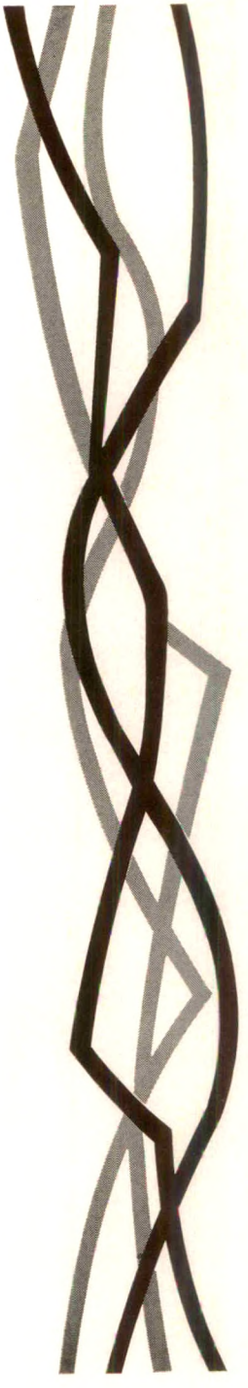
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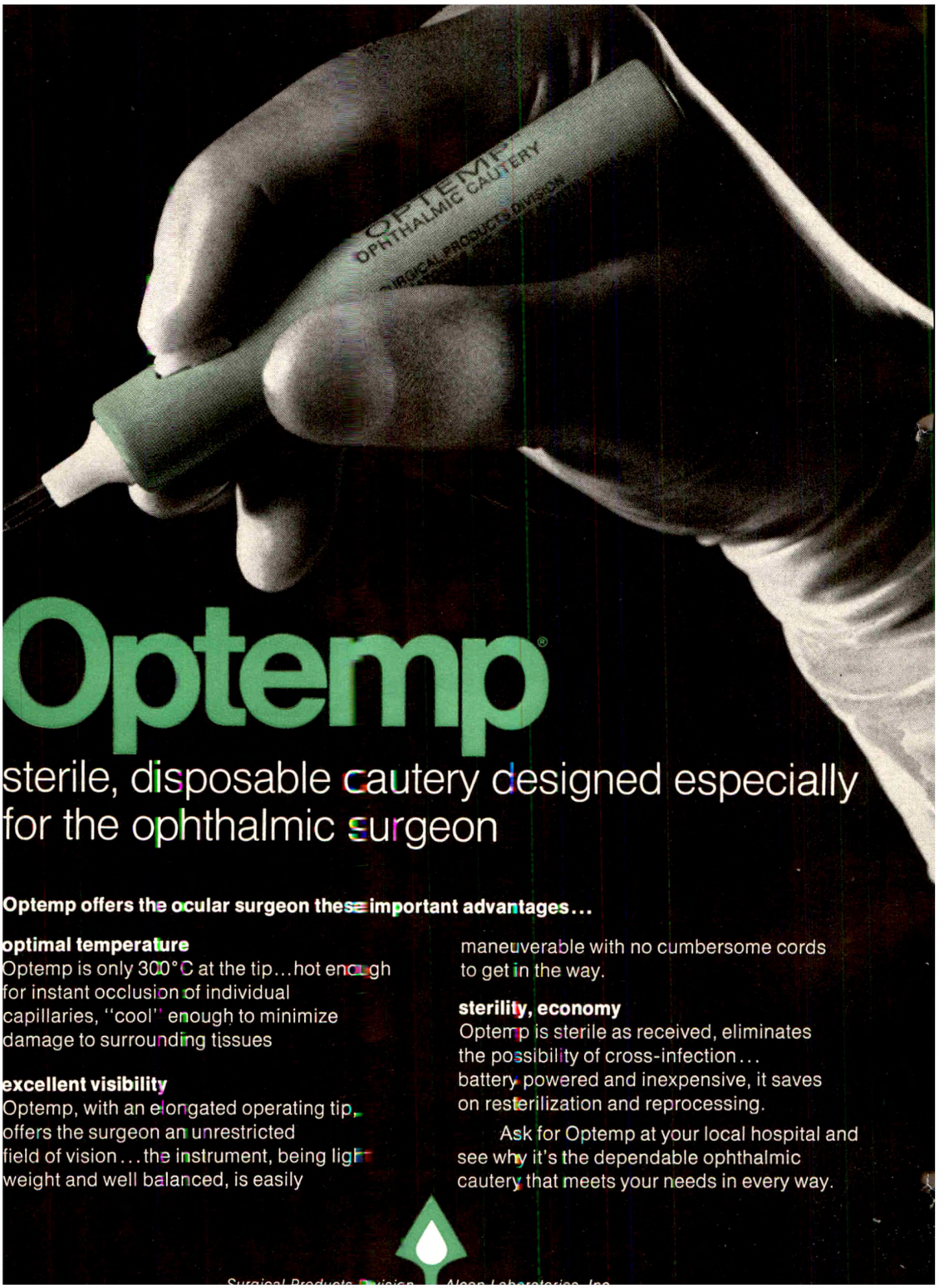
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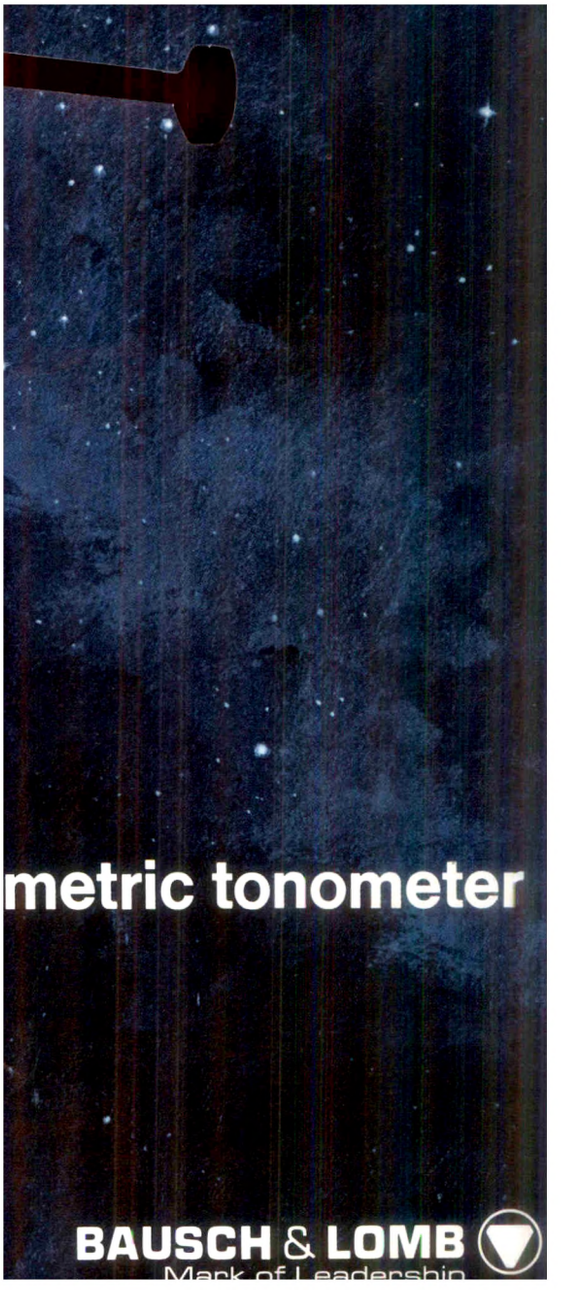
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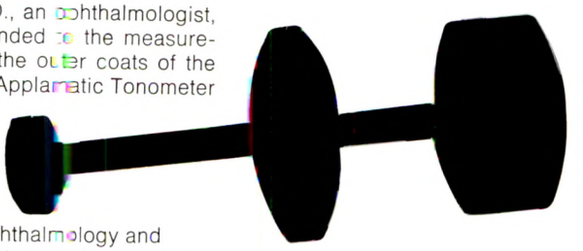

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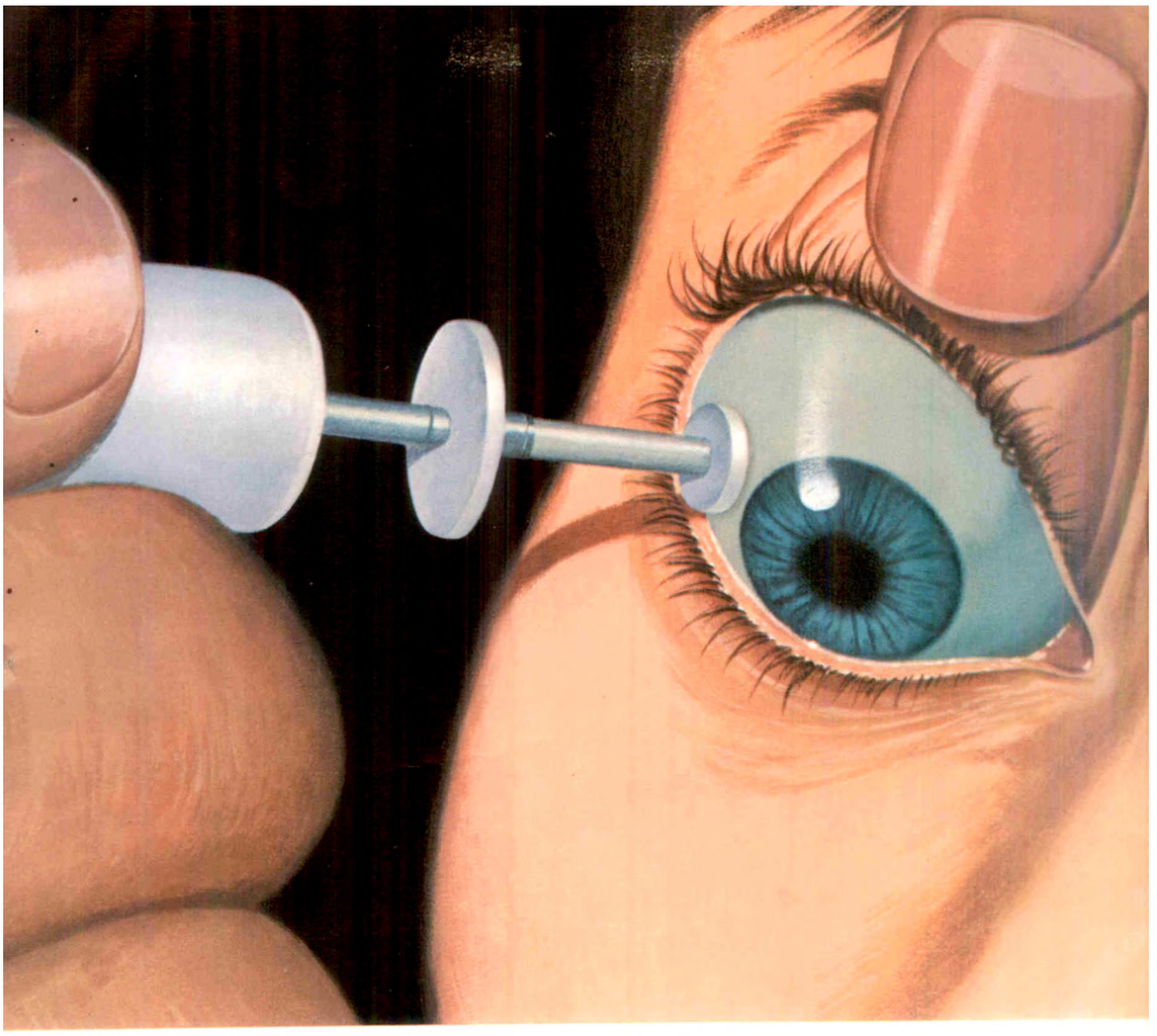
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# Jet or Drop

***DACRIOSE gives you complete control of ocular irrigation. You can provide a gentle but thoroughly cleansing "jet-like" action . . . or you can use it drop-by-drop.***

This modern irrigating solution, in the unique *Jet-Stream* dispenser, is ready-to-use and self-sterilizing.

Use DACRIOSE

☐ *In the office:* after tonometry and gonioscopy — to wash away fluorescein — to wash out secretions and discharges.

☐ *In the emergency room:* for quick, safe removal of foreign bodies.

☐ *In the operating room:* for sterile and convenient irrigation of the eye pre- and post-operatively.

☐ *At the bedside:* to clean and irrigate eyes — to save staff time.

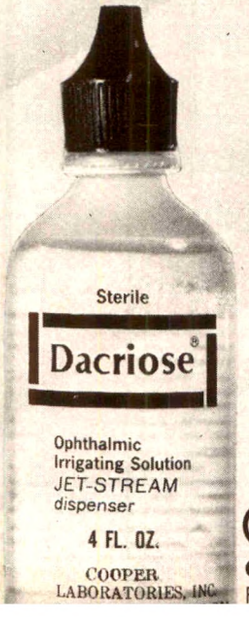
**Formula:** A sterile, stable, buffered isotonic solution of boric acid, sodium carbonate, potassium chloride. Preserved with benzalkonium chloride, 0.01%; with 0.01% disodium ethylenediamine tetraacetate.

**Warning:** Do not dilute or reuse the solution. Do not touch dropper tip to eye or any surface as this may contaminate solution.

**Supply:** 0.95 fl. oz. and 4 fl. oz. plastic Irrigator bottles.

## DACRIOSE®

you control the flow — sterile and self-sterilizing — isotonic




Cooper

**COOPER LABORATORIES, INC.**
Fairfield Road, Wayne, New Jersey 07470

# THE 10 MOST QUESTIONS ABOUT

## THE QUESTIONS

1. What makes PHOTOGRAY lenses work?
2. How fast do PHOTOGRAY lenses change?
3. Will the darkening-fading process wear out?
4. Do PHOTOGRAY lenses need breaking in?
5. Can PHOTOGRAY lenses be hardened or toughened?
6. How do PHOTOGRAY lenses work in a car?
7. In what types of lenses is PHOTOGRAY glass available?
8. Is the darkening-fading process comfortable to the wearer?
9. Do PHOTOGRAY glasses have a residual tint indoors?
10. Will PHOTOGRAY glass be available in a darker sunglass version?

**Note:** If you get asked other questions by your patients about PHOTOGRAY glasses that you think would be of broad interest, please send them to us. When we get enough new ones, we'll answer them in another ad.

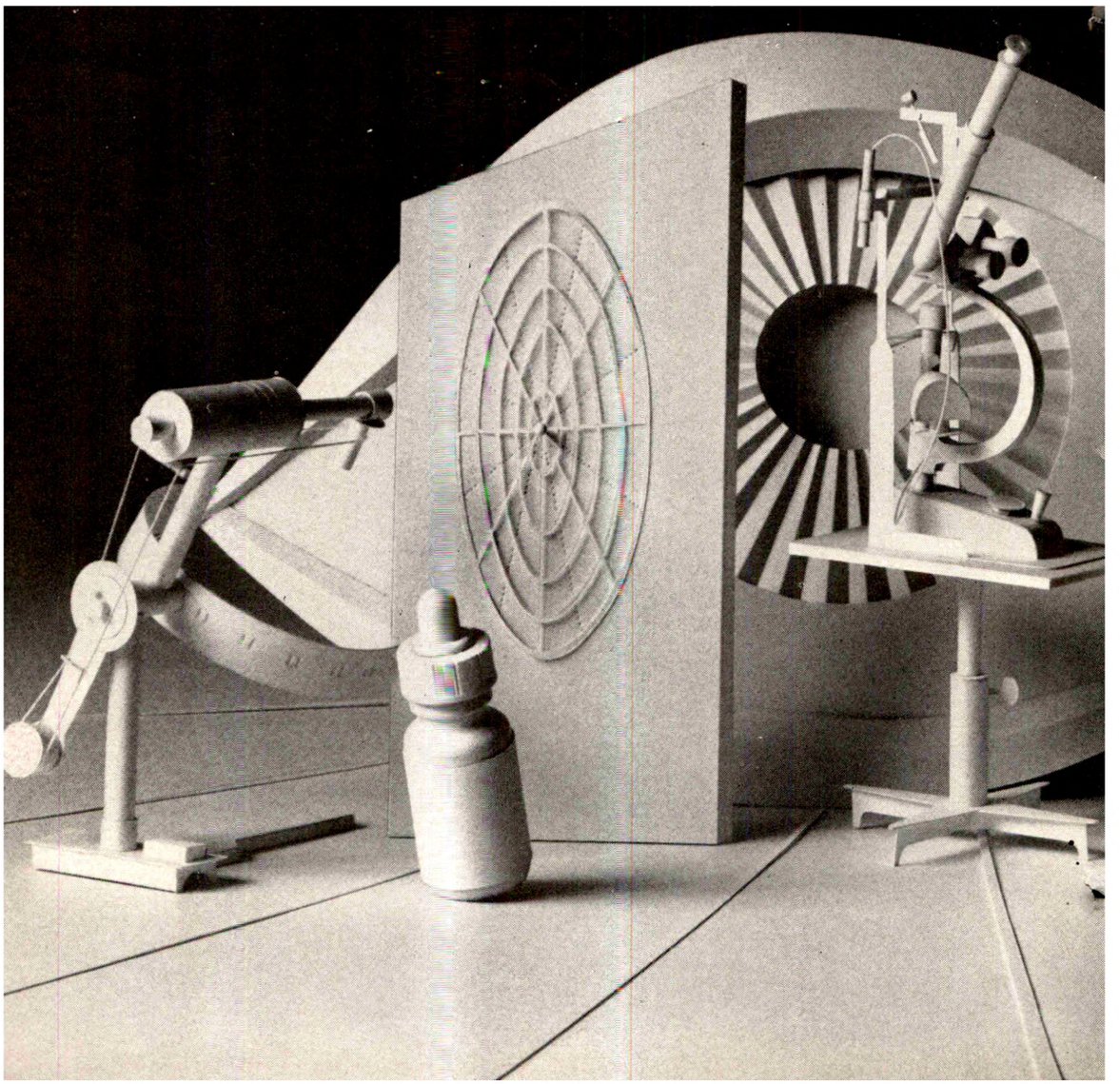
If you'd like complete technical information on PHOTOGRAY lenses, just write to: Corning Optical Products Dept., Corning, New York 14830.

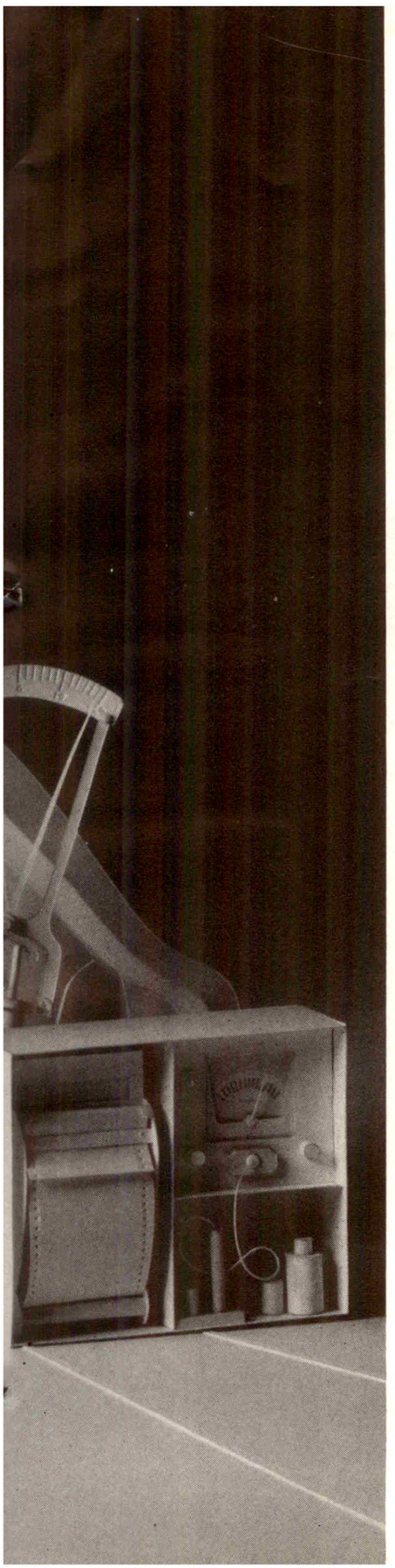
# FTEN ASKED
# PHOTOGRAY® LENSES.

## THE ANSWERS

1. PHOTOGRAY lenses are photochromic: sensitive to ultraviolet light. When sunlight strikes them, invisible microcrystals of silver halide become darkened. When the light is removed, the crystals clear again.
2. Quite rapidly. In 60 seconds the lens is 75% darkened by sunlight and virtually fully darkened in 5 minutes. Removed from sunlight the lens clears half way in 5 minutes and 75% in 20 minutes. At their darkest, PHOTOGRAY lenses have a light transmittance of 45%. When clearest they have a light transmittance of 85%.
3. No. The photochromic reaction is locked into the composition of the glass and is completely reversible. It will keep performing for a lifetime without changing its characteristics.
4. Yes. Several complete darken-fade cycles are needed to bring PHOTOGRAY lenses up to their normal operating performance.
5. Yes, Most definitely. PHOTOGRAY lenses can be heat-treated or tempered. The tempering time is slightly different from that needed for clear lenses. Corning publishes heat-treating tables that give settings for the more popular units available.
6. Not too well. The window glass will screen out a lot of the ultraviolet light which activates the photochromic property of the lenses. This keeps the glass from darkening as fully as when it is exposed to direct sunlight.
7. PHOTOGRAY lenses come in a full range of sizes—in both single-vision and 1 piece multi-focal types.
8. Yes. The process, while quite rapid, is gradual enough to be imperceptible to the wearer. This, combined with the protection given by the darkened glass, is why PHOTOGRAY is known as the "comfort glass".
9. Yes. It's a very light, hardly noticeable tint.
10. Yes. Corning is currently in the final stages of developing a sunglass companion to PHOTOGRAY glass. Called PHOTOSUN™ glass, it's a true variable sunglass. PHOTOSUN lenses will be ready for introduction shortly.

CORNING
OPTICAL PRODUCTS





# When epinephrine is indicated for the management of chronic simple (open-angle) glaucoma

# Ayerst Epitrate® BRAND OF epinephrine bitartrate

BRIEF SUMMARY

*(For full prescribing information, see package circular.)*

**Epitrate**® (epinephrine bitartrate)

***For management of chronic simple (open-angle) glaucoma***

**Description:** A sterile aqueous solution of levorotatory epinephrine bitartrate 2% (equivalent to 1.1% base), it is stable, retains its potency throughout use, and requires no refrigeration. It has a low surface tension.

**Action:** Intraocular pressure is lowered by reducing the rate of aqueous formation. Improvement in outflow facility is also observed in certain cases following prolonged therapy.

**Indications:** Useful in management of chronic simple (open-angle) glaucoma, either alone or in combination with miotics. In selected cases, it may also be used with carbonic anhydrase inhibitors.

**Contraindications:** Prior to peripheral iridectomy, an epinephrine preparation is contraindicated in eyes that are capable of angle closure since its relatively weak mydriatic action may, nevertheless, precipitate angle block. Gonioscopy should be carried out on all patients before initiating therapy.

**Warnings:** Topical use of epinephrine in any form should be interrupted prior to general anesthesia with certain anesthetics such as cyclopropane or halothane which sensitize the myocardium to sympathomimetics.

**Precautions:** EPITRATE (epinephrine bitartrate) should be used with caution in the presence of hypertension, diabetes, hyperthyroidism, heart disease, and cerebral arteriosclerosis because of the possibility of systemic action.

**Adverse Reactions:** As with other epinephrine solutions, transitory stinging on initial instillation may be expected. Headache or browache frequently occur on beginning EPITRATE therapy, but usually diminish as treatment is continued. Conjunctival allergy occurs occasionally. Pigmentary deposits in the lids, conjunctiva or cornea may occur after prolonged use of epinephrine eyedrops. In rare cases, maculopathy with a central scotoma may result from the use of topical epinephrine in aphakic patients; prompt reversal generally follows discontinuance of the drug. Systemic effects have occasionally been reported, such as: palpitation, tachycardia, extrasystoles, hypertension, trembling, sweating, and pallor.

**Dosage and Administration:** 1 drop, with frequency of instillation being individualized, from every two or three days to twice daily. More frequent instillation than one drop four times daily does not usually elicit any further improvement in therapeutic response.

**How Supplied:** No. 1015—EPITRATE—ophthalmic solution of epinephrine bitartrate 2% (equivalent to 1.1% base). [Also contains chlorobutanol (chloral derivative) 0.5%, methylaminoaceto pyrocatechol HCl, sodium bisulfite, sodium chloride, polyoxypropylene-polyoxyethylene-diol, and disodium edetate.] Package containing 7.5 cc. bottle with separate dropper-screw cap attachment.

The Ophthalmos Division
**AYERST LABORATORIES**
New York, N.Y. 10017

7141

# NEW DEVELOPMENTS . . .

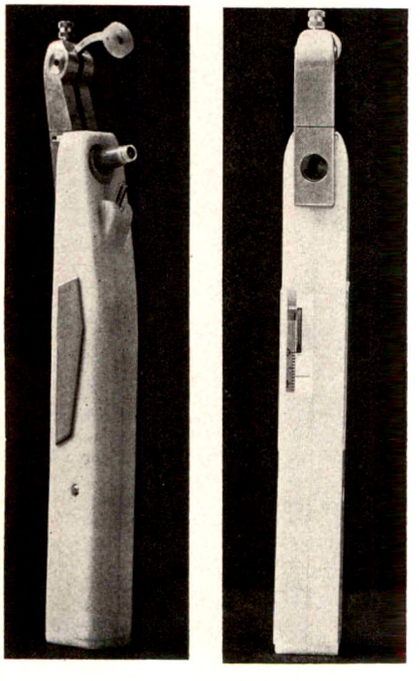


## ORA SERRATA ATTACHMENT TO THE GOLDMANN 3 MIRROR LENS

The periphery of the fundus near the ora serrata and the ciliary body cannot be examined under normal conditions with the 3-mirror lens alone. The ora serrata attachment along with the 3-mirror lens allows the observation of these most peripheral parts in its entire circumference.

The attachment is shaped like the 3-mirror lens. Half a steel-ball is fixed to the scleral part of the attachment which presses on the sclera above the ora serrata so that the fundus at its periphery near the ora serrata can be seen in the gonio mirror of the 3-mirror lens. The ora attachment can be used either with the 3-mirror lens in a locked or moveable position.

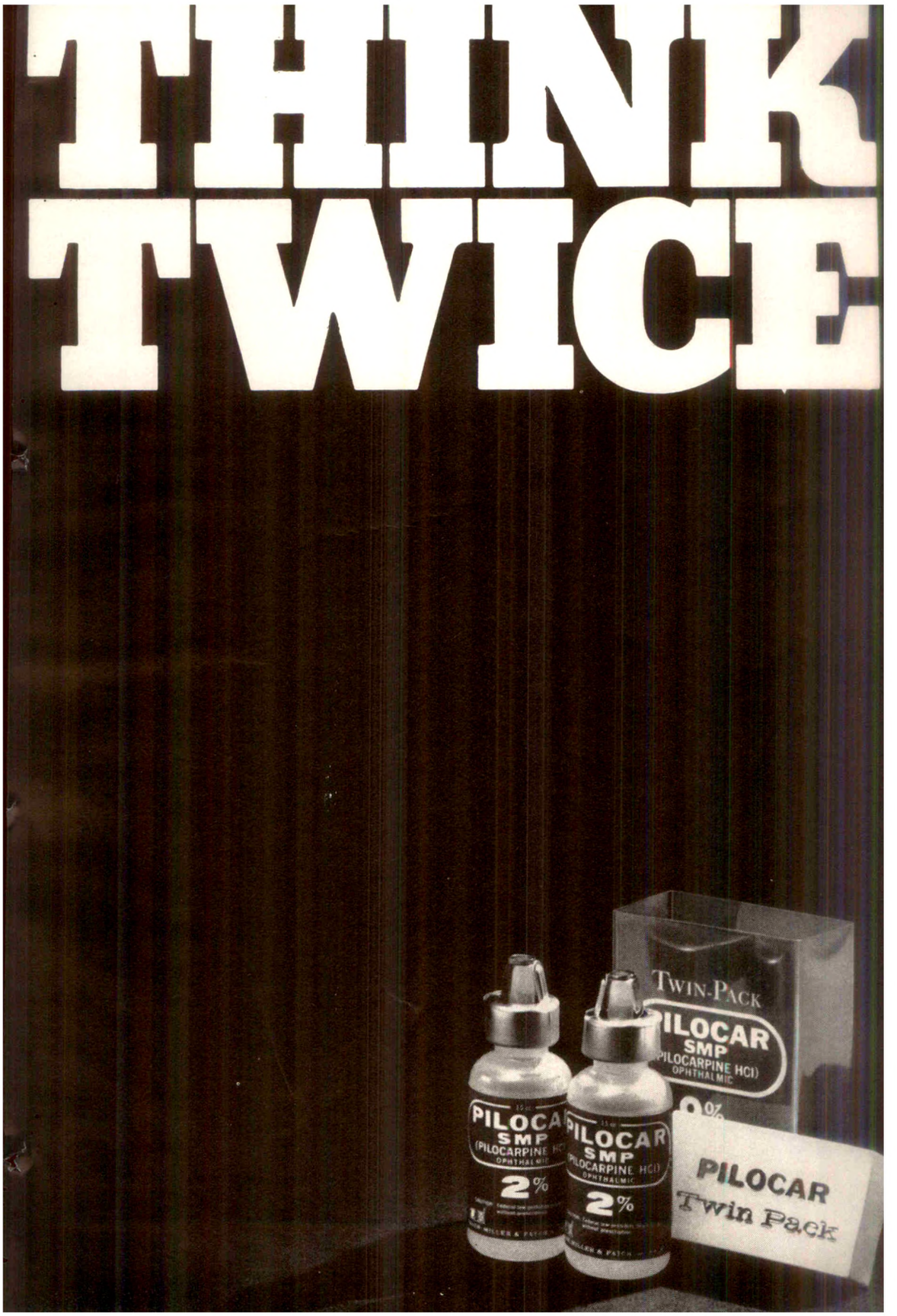
## THE PERKINS HAND HELD APPLANATION TONOMETER



- LIGHT WEIGHT
- GOLDMANN PRISM
- EASY TO USE

GRIESHABER SURGICAL INSTRUMENTS
(MADE IN SWITZERLAND)

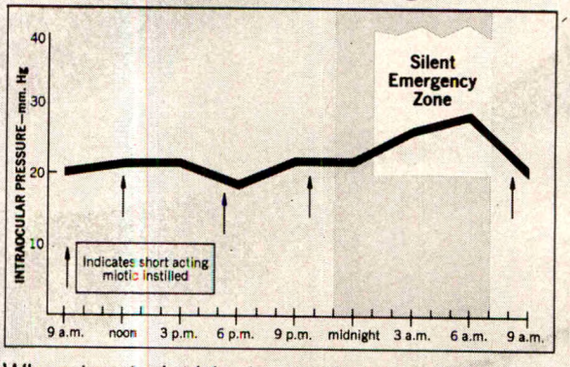
**ALFRED P. POLL, INC.**
THE HOUSE OF QUALITY OPTICS
40 WEST 55 STREET NEW YORK, NY 10019


THINK
TWICE
TWIN-PACK
ILOCAR
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PILOCARPINE HCl)
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OPHTHALMIC
2%
PILOCAR
SMP
(PILOCARPINE HCl)
OPHTHALMIC
2%
PILOCAR
Twin Pack

# Not more potent, but longer acting*...

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

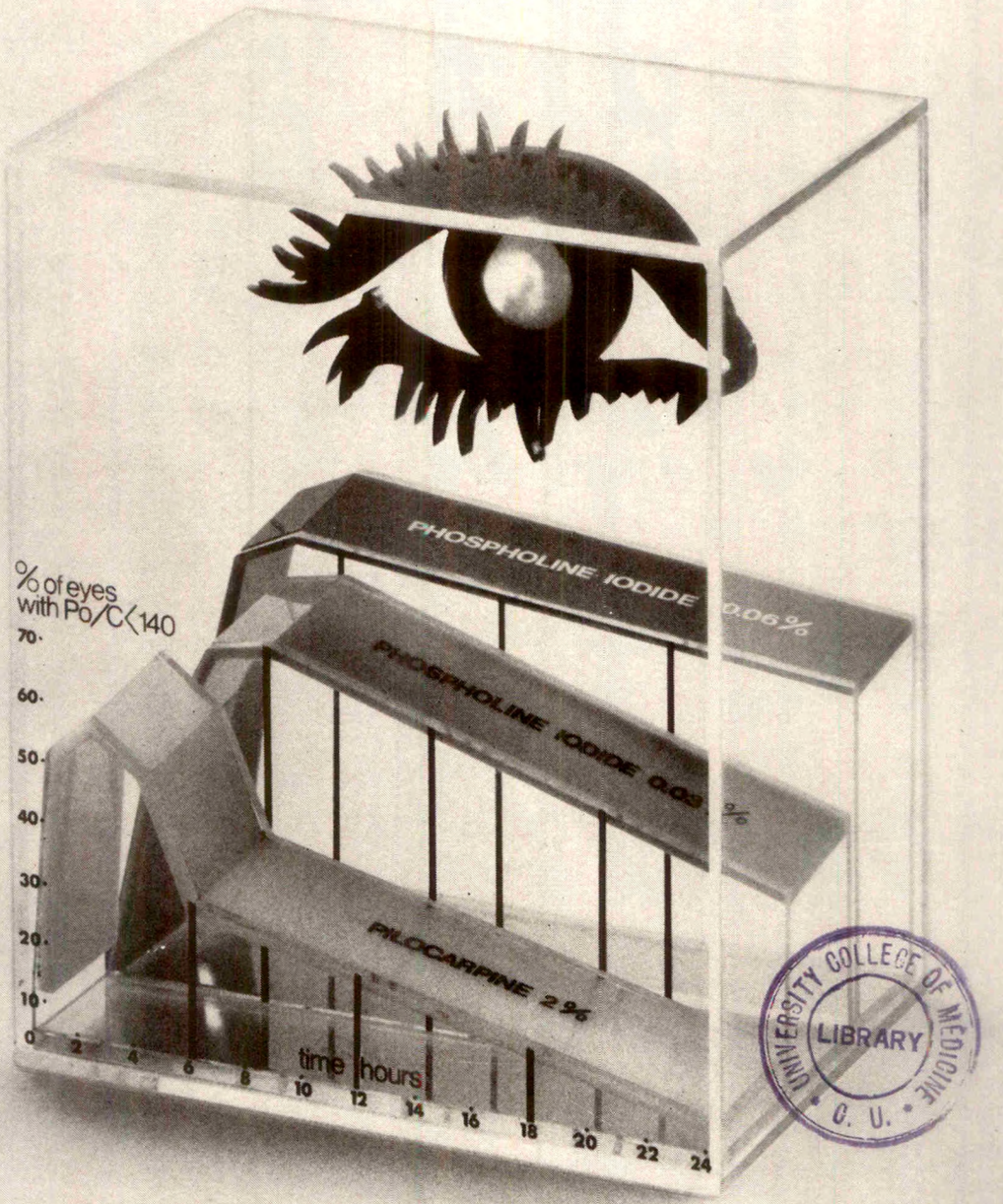



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25% —when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




UNIVERSITY COLLEGE OF MEDICINE
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G. U.

Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

for 24 hour control in chronic simple (open-angle) glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, browache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

# The new Zeiss Zoom OpMi 7... a true ophthalmological specialist.

The new OpMi 7 is truly special in every sense of the word. It's special in that it is designed only for ophthalmological microsurgery. And special too in price—its many outstanding design features are shared only with instruments costing considerably more.

**Wide field of view:** 55 mm at 3.6x — 95% more area than other instruments in its price range.

**Building block design:** it accepts all the valuable Zeiss accessories, including the Beam Splitter System for still and motion picture photography and TV, the unique high-eyepoint eyepieces for spectacle wearers, a fiber-optic "cool-light" illumination system, the assistant's stereo microscope with the same high quality optics as the surgeon's, and the 2x operating field magnifier.

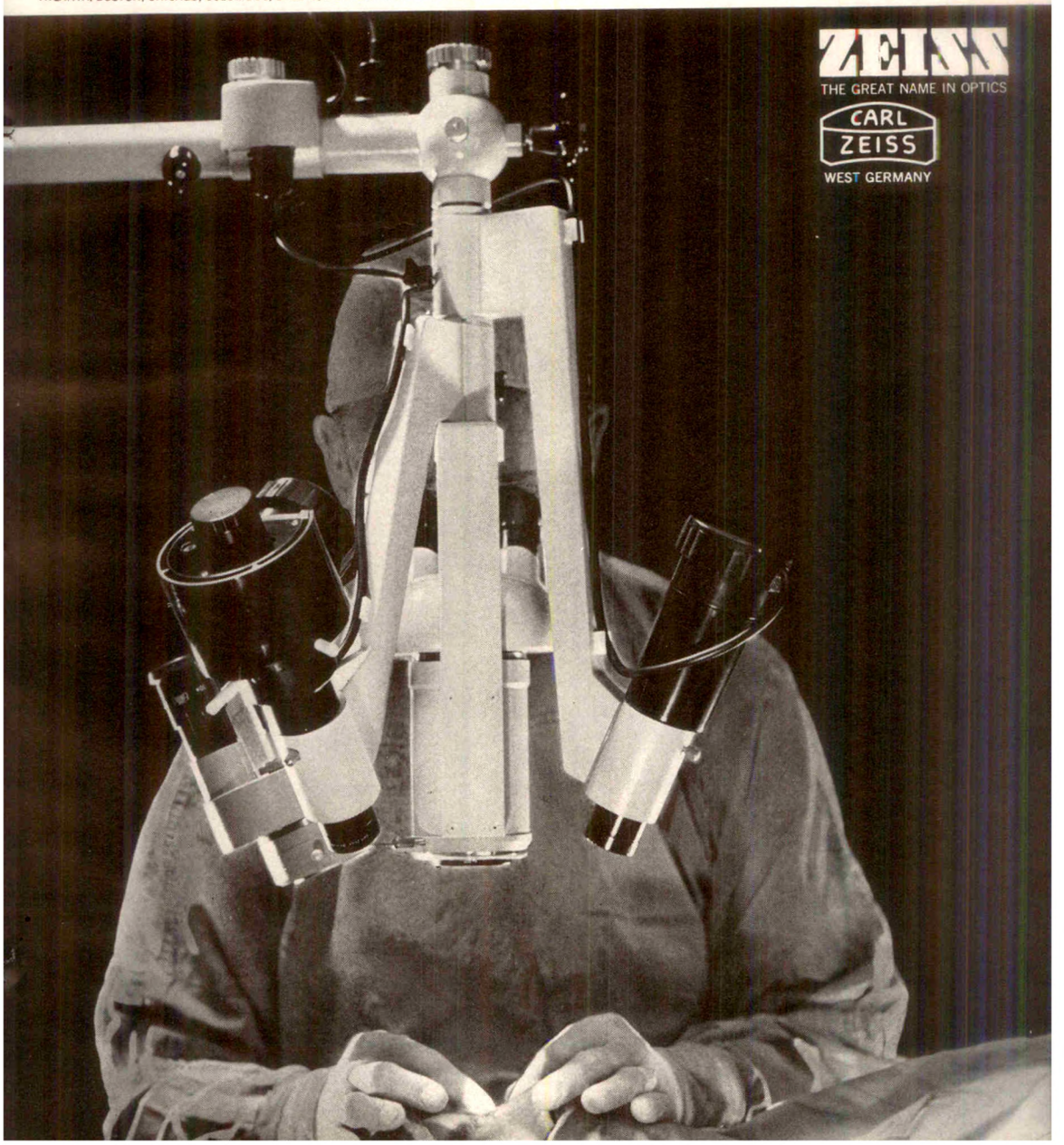
**Choice of 3 stands:** including the new Ceiling Suspension System.

**Choice of 3 working distances:** 6", 7" or 8" to your specification.

That's only a start. For complete details, write or call Carl Zeiss, Inc., 444 5th Ave., New York, N. Y. 10018. (212) 736-6070.

Nationwide Service.

ATLANTA, BOSTON, CHICAGO, COLUMBUS, DALLAS, DENVER, HOUSTON, KANSAS CITY, LOS ANGELES, PHILADELPHIA, PHOENIX, SAN FRANCISCO, SEATTLE, WASHINGTON, D.C.

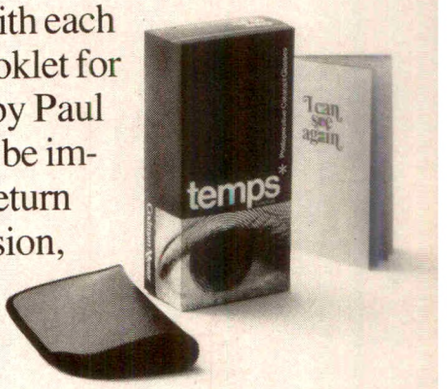


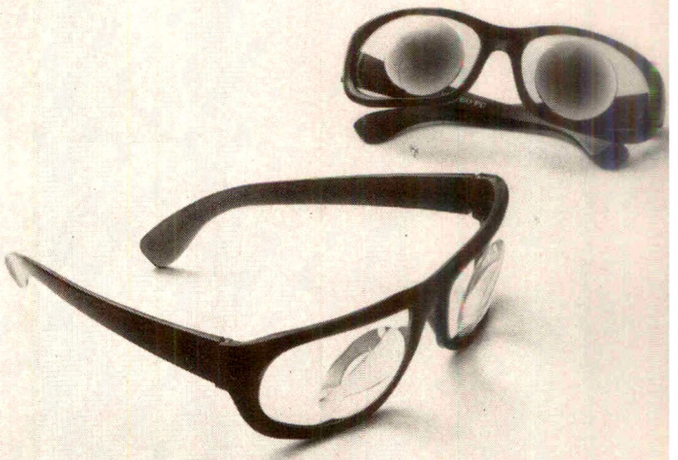


# Behind the smile . . . a new lease on life.

Temps* glasses help post cataract recovery with their cosmetically attractive shape, their lightness, and their protectiveness. Clear or tinted, the excellent optics are the thinnest, least distorting of the temporaries – perfectly adequate for spares later on. Available in wide or narrow P.D. (63 to 68mm, 57 to 62mm), bifocal or single vision.

We invite you to try six pairs of Temps glasses, or six Day-Nite Paks (clear and tinted pairs together, economically priced). Included with each is a carrying case and a helpful booklet for your patient, "I Can See Again," by Paul Tisher, M.D. We're sure you will be impressed by Temps glasses, a full return refund if you're not. Mentor Division, Codman & Shurtleff, Inc., Randolph, Mass. 02368.



Codman Mentor
DIVISION

*TM © 1970 by Codman & Shurtleff, Inc.

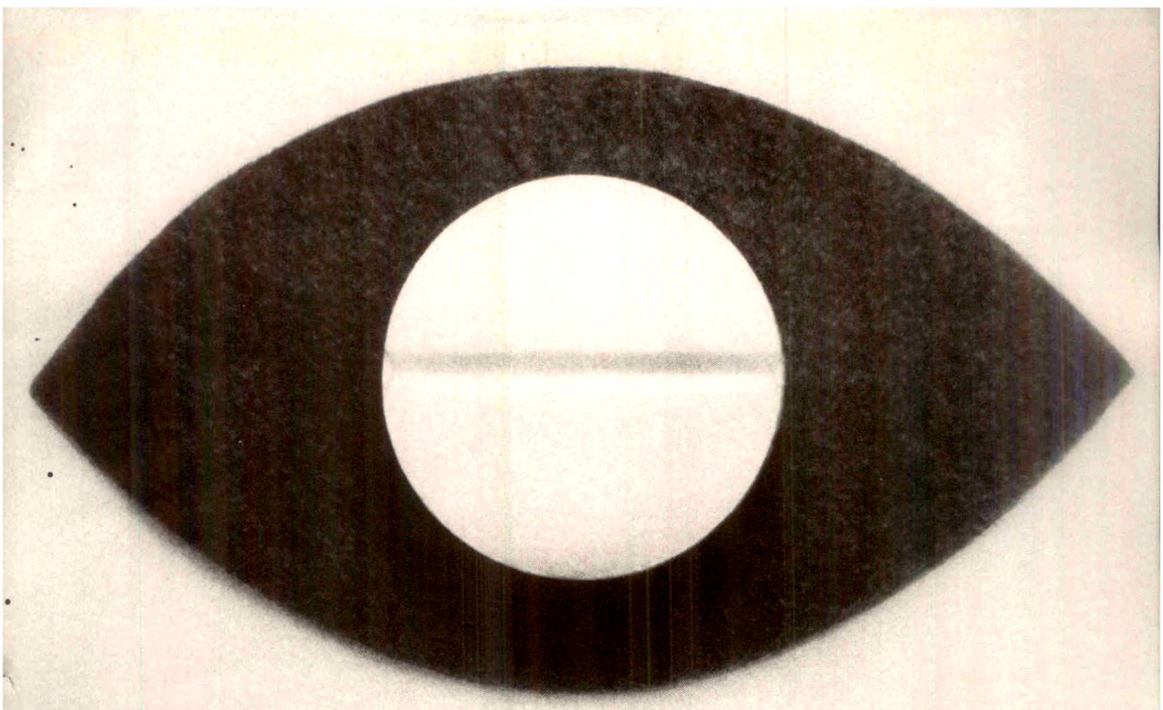



# BY ALL MEANS!

Armorlite originated the world's first hard resin lenses in 1947 and has been perfecting them ever since. We make more types of these modern lenses than any one else, and they have a reputation for unsurpassed quality. We make only hard resin lenses and we do it in earnest; they are not a side-line with us.

When you think patient care and protection, think Armorlite, by all means.

**ARMORLITE, INC.**



THE NEXT LOGICAL STEP IN GLAUCOMA THERAPY...
if patients become refractory or intolerant to acetazolamide

# NEPTAZANE® Tablets
## Methazolamide, 50 mg.

also an outstanding anti-glaucoma drug

For patients who can no longer be effectively controlled with acetazolamide—or cannot tolerate it over an extended period—NEPTAZANE Methazolamide is the next logical therapeutic step. Logical, because NEPTAZANE Methazolamide and acetazolamide are equally effective as ocular tension reducers due to their identical mode of action. So, with NEPTAZANE Methazolamide available as an alternate carbonic anhydrase inhibitor, it is possible for you to switch when necessary, and control many cases on long-term glaucoma therapy.

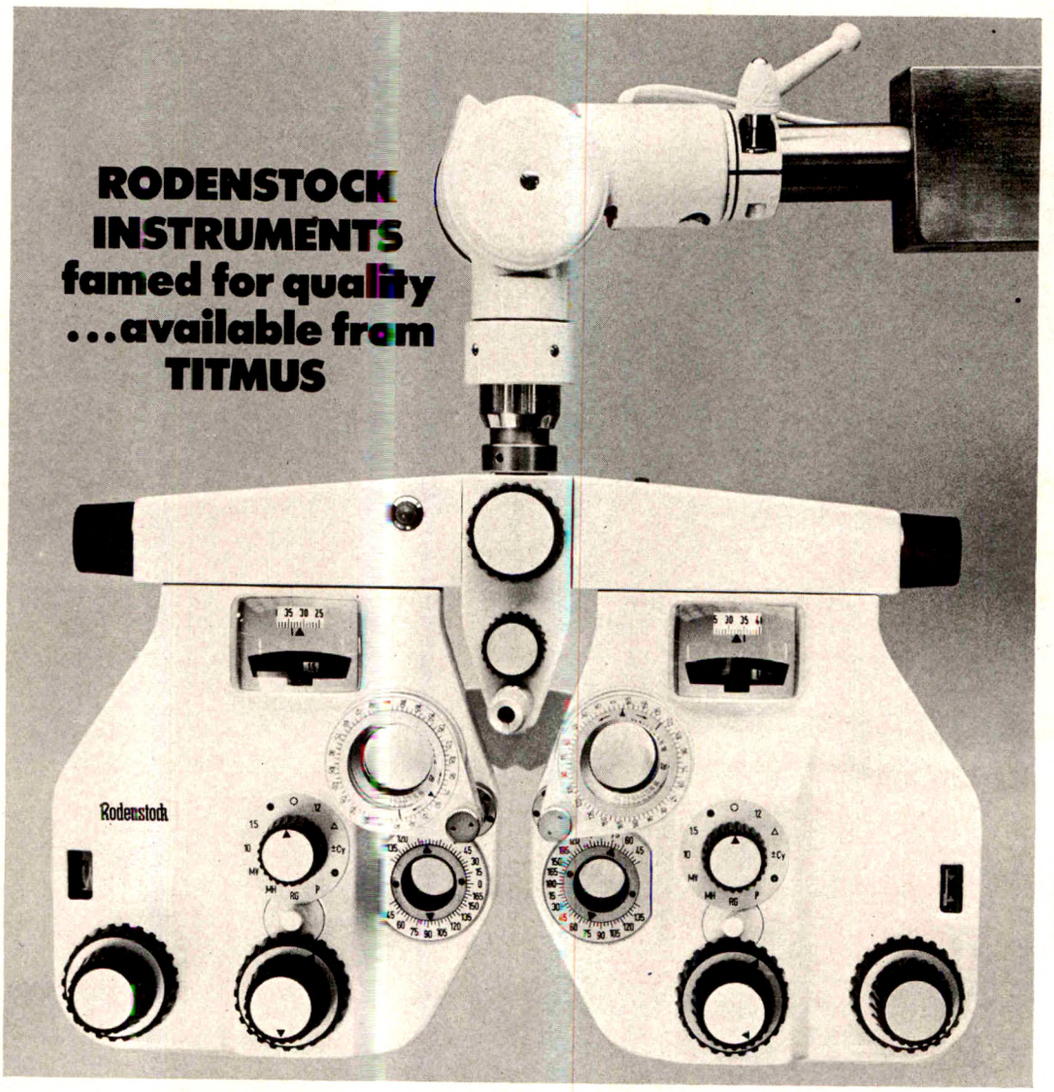
**Contraindications:** Severe (absolute) or hemorrhagic glaucoma; chronic noncongestive angle-closure glaucoma; adrenocortical, hepatic, or renal insufficiency; electrolyte imbalance states; sodium and potassium depletion states.

**Warning:** Although teratogenic effects demonstrated in rats at high doses have not been evidenced in humans, Methazolamide should not be used in women of childbearing age or in pregnancy, especially in the first trimester, unless the expected benefits outweigh these potential adverse effects.

**Precautions:** Use with caution in patients with cirrhosis or hepatic insufficiency to forestall hepatic coma; those on steroid therapy; those with pulmonary obstruction or emphysema. Electrolyte balance should be maintained. Although not reported thus far with this drug, reactions common to sulfonamide derivatives, such as fever, leukopenia, hemolytic anemia, bone marrow depression or renal calculi, may occur.

**Adverse Reactions (mostly mild and dose-related):** anorexia, nausea, vomiting; malaise, fatigue, drowsiness, headache, vertigo, mental confusion, depression; paresthesia. Urinary citrate excretion and uric acid output is decreased during use of this drug, but urinary calculi have not been reported.

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965
367-1




# Rodenstock Phorovist

Sealed construction eliminates costly cleaning.

Monocular PD Control. Also vertical asymmetry adjustment.

Internal illumination makes cumulative power readings easy to see—even in darkened room.

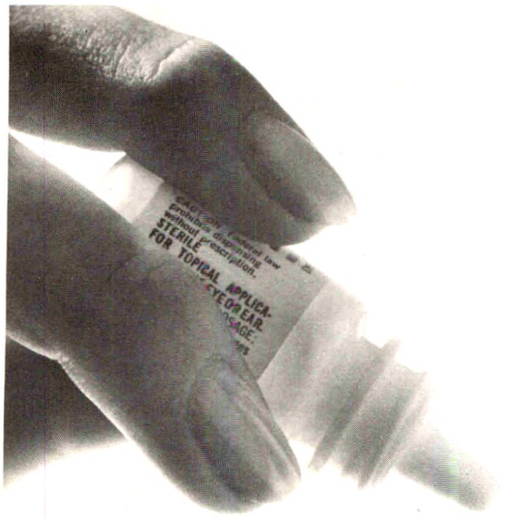
Positive corneal vertex distance control eliminates guesswork.

Other fine Rodenstock instruments available from Titmus include:
Rodavist Projector
Refractometer
Lensometer
Slit Lamp
Projection Perimeter

TITMUS
OPTICAL CO., INC., PETERSBURG, VA. 23803


Most ophthalmic solutions start out sterile. But the OCUMETER® helps this one stay that way.
OCUMETER helps steroid solution stay sterile by eliminating a major cause of contamination —the eye dropper. Sterile, highly stable
Ophthalmic Solution
DECADRON®
Phosphate
(Dexamethasone Sodium Phosphate, MSD)
0.1% Dexamethasone Phosphate Equivalent
for mild acute iritis and nonpurulent conjunctivitis
For prescribing information, please see next page.

## for mild acute iritis and nonpurulent conjunctivitis




Sterile, highly stable
Ophthalmic Solution
**DECADRON**® Phosphate
(Dexamethasone Sodium
Phosphate | MSD)

Not all steroid ophthalmic solutions stay sterile during the days and weeks of therapy. But this one is more apt to—Ophthalmic Solution DECADRON Phosphate (Dexamethasone Sodium Phosphate, MSD) in the OCUMETER® eliminates a common source of contamination—the eye dropper.

*Uniform dosage, drop after drop*

Each drop of Ophthalmic Solution DECADRON Phosphate contains the same dosage of steroid. And, with a gentle squeeze, the OCUMETER measures out one drop at a time. So your patient can conveniently get the steroid dose you want her to have, wherever she is.

Each cc. contains dexamethasone sodium phosphate equivalent to 1 mg. (0.1%) dexamethasone phosphate. Also available as DECADRON® Phosphate Ophthalmic Ointment (0.05%); and as NeoDECADRON® Ophthalmic Solution containing dexamethasone sodium phosphate equivalent to 1 mg. (0.1%) dexamethasone phosphate and neomycin sulfate equivalent to 3.5 mg. neomycin base in each cc.; and NeoDECADRON® Ophthalmic Ointment, containing dexamethasone sodium phosphate equivalent to 0.5 mg. (0.05%) dexamethasone phosphate and neomycin sulfate equivalent to 3.5 mg. neomycin base per gram.

CONTRAINDICATIONS: DECADRON and NeoDECADRON should not be used in the presence of infectious tuberculous lesions of the eye, chickenpox, early acute herpes simplex, vaccinia, the early acute stages of most viral diseases of the cornea and conjunctiva, acute purulent untreated infections of the conjunctiva and lids, suspected ocular or aural fungal infection, perforated ear drum. Sensitivity to components is also a contraindication.

PRECAUTIONS: DECADRON: Like all adrenal corticosteroids, may sometimes mask, activate, or enhance incipient infection. Whenever possibility of infection exists, suitable antibiotic agents or a steroid-antibiotic preparation (such as NeoDECADRON) should be considered. If infections do not respond promptly, therapy should be discontinued until the infection has been adequately controlled by other measures.

Systemic side effects may occur with extensive use of steroids. Rarely, ocular herpes simplex has been reported in patients receiving adrenocortical steroids systemically or locally in the eye for other conditions.

As with other corticosteroids, increased intraocular tension can follow extended local use (1-2 weeks or more) of dexamethasone sodium phosphate. Since increased intraocular tension can lead to loss of vision, this possibility should be kept in mind and topical administration used only under adequate tonometric supervision, particularly in patients known to have glaucoma, or whose family history includes glaucoma.

In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. Reports in the literature indicate that, rarely, protracted use of topical corticosteroids in the eye may be associated with the development of posterior subcapsular cataracts. Hereditary and degenerative eye diseases in general do not show any response to treatment with these preparations.

Stubborn cases of anterior segment eye disease may require systemic adrenocortical hormone therapy. When the deeper ocular structures are involved, systemic therapy is necessary.

NeoDECADRON: A few individuals may be sensitive to one or more of the components of NeoDECADRON. If any reaction indicating sensitivity is observed, discontinue use. Sensitivity to neomycin may occasionally develop, especially when it is applied to abraded skin. Some reports in the current literature point to an increase in the number of persons sensitive to neomycin.

Use of any antibiotic agent may result in overgrowth of fungi or other organisms not susceptible to the antibiotic, necessitating prompt medical attention for such new infections.

As the safety of topical steroids during pregnancy has not been confirmed, they should not be used for extended periods during pregnancy.

**For more detailed information, consult your MSD Representative or see the Direction Circular. Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa. 19486**

**MSD** MERCK SHARP & DOHME

# A singular new antibiotic for the eye that works the way you think it should

## GARAMYCIN® brand of GENTAMICIN SULFATE OPHTHALMIC SOLUTION/OINTMENT



Each cc. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

## You think it should have a wide antibacterial spectrum

GARAMYCIN's wide range of antibacterial action is equal to the spectrum commonly prescribed in the combinations of neomycin, polymyxin and bacitracin or gramicidin in the treatment of external eye infections due to susceptible organisms. It has activity against a wide variety of both gram-positive and gram-negative organisms, including the "difficult" ones—*Pseudomonas aeruginosa* strains and Proteus.

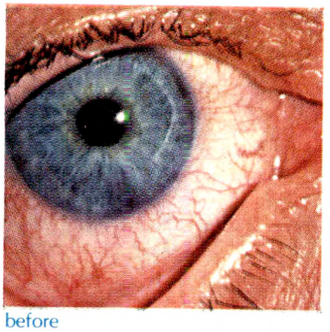
## You think it should be a single entity antibiotic

GARAMYCIN is a single entity antibiotic with a low incidence of sensitization or resistance*—can be used repeatedly with continued effectiveness, less concern about allergic potential (*Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.)

## You think it should be clinically effective

GARAMYCIN OPHTHALMIC has been described as appearing to be "...an antibiotic of choice for the initial treatment of external ocular infections."[1] It has "proved highly effective...for a wide variety of common bacterial eye infections..."[2] (due to susceptible organisms).
(1. Gordon, D.M.: Amer. J. Ophthal. 69:300 [Feb.] 1970. 2. Magnuson, R. H., and Suie, T.: JAMA 199:427 [Feb. 6] 1967.)

In acute catarrhal conjunctivitis and episcleritis† due to *Staphylococcus aureus* coagulase negative



before

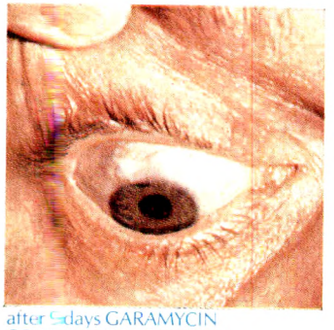


after 7 days GARAMYCIN OPHTHALMIC SOLUTION

In infected bleb (post-glaucoma surgery)† due to *Staphylococcus aureus* coagulase negative and *Streptococcus viridans*

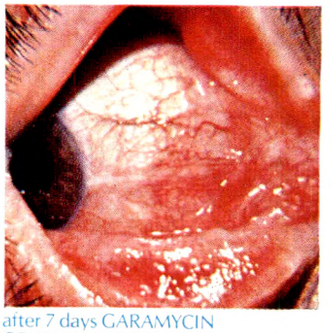


before

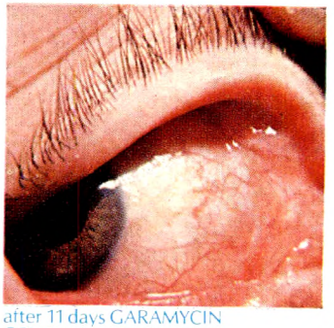


after 5 days GARAMYCIN OPHTHALMIC SOLUTION

In acute conjunctivitis and dacryocystitis†† due to pneumococcus



after 7 days GARAMYCIN OPHTHALMIC SOLUTION



after 11 days GARAMYCIN OPHTHALMIC SOLUTION

# New GARAMYCIN® ophthalmic

brand of
GENTAMICIN SULFATE SOLUTION/OINTMENT

†Photographs courtesy of D. Gordon, M.D., N.Y., N.Y. ††Photographs courtesy of S. Fox, M.D., Baltimore, Md.

# You think it should have flexibility in dosage forms

GARAMYCIN OPHTHALMIC SOLUTION, sterile, isotonic, and buffered to pH of tears, does not blur vision, is well suited to daytime use—supplied in an unbreakable, easy-to-handle dispenser.

GARAMYCIN OPHTHALMIC OINTMENT provides gentle emollient action and keeps medication in contact with tissues for longer periods. It is particularly advantageous for nighttime use or in non-ambulatory patients—supplied in easy-to-use ophthalmic tube.

## Clinical Considerations

**Description:** GARAMYCIN is an antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN Ophthalmic Solution is a sterile aqueous solution buffered to approximately pH 6.7 for use in the eye. Each cc. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN Ophthalmic Ointment contains, in each gram of ointment, gentamicin sulfate (equivalent to 3.0 mg. gentamicin), and methylparaben and propylparaben as preservatives in a bland base of clear petrolatum.

Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

**Indications:** GARAMYCIN Ophthalmic Solution and Ointment are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

**Contraindications:** GARAMYCIN Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of the components of these preparations.

**Precautions:** Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

**Dosage and Administration:** GARAMYCIN Ophthalmic Solution: One or two drops every four hours. In severe infections, dosage may be increased to as much as two drops once hourly.

GARAMYCIN Ophthalmic Ointment: Apply a small amount to the affected eye two to three times daily.

**How Supplied:** GARAMYCIN Ophthalmic Solution, 5 cc. plastic dropper bottle, sterile, box of 1. GARAMYCIN Ophthalmic Ointment, 1/8 ounce tube, box of 1.

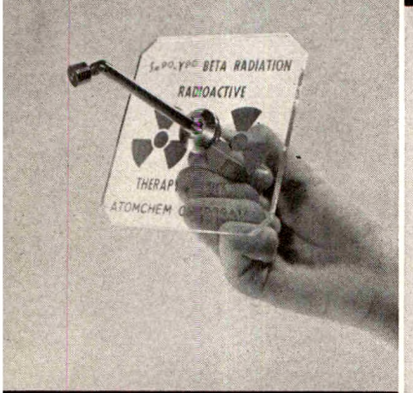
Note: Store away from heat.

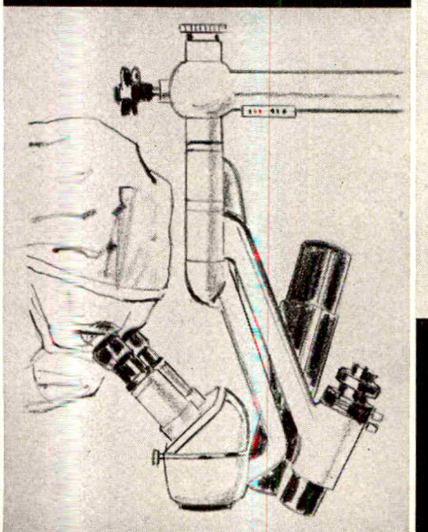


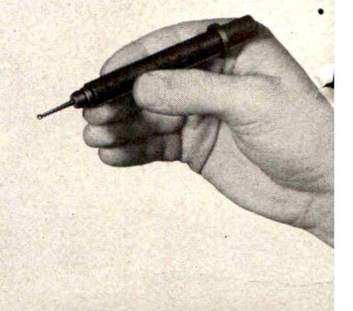

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# Look at all three





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And now HUMORSOL is available in an improved dispenser—the easy-to-use, nonbreakable plastic OCUMETER® with a metered tip to help assure that your patient gets the precise dosage you prescribe.

In addition, the Direction Circular has been significantly revised. We urge you to consult it before prescribing.

We emphasize, however, that the formulation, Ophthalmic Solution HUMORSOL, remains exactly the same.

Supplied in two dosage strengths, 0.125 percent and 0.25 percent, each in a 5-cc OCUMETER® Ophthalmic Dispenser, with benzalkonium chloride 1:5000 added as preservative.

**For additional prescribing information, please see following page.**

# HUMORSOL® (DEMECARIUM BROMIDE | MSD) IS BACK

in OCUMETER® Ophthalmic Dispensers for greater accuracy and patient-convenience




## REVISED PRESCRIBING INFORMATION

**FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY**

**Indications:** Open-angle glaucoma; conditions obstructing aqueous outflow that are amenable to miotic therapy, such as synechial formation; following iridectomy; accommodative esotropia (accommodative convergent strabismus).

**Contraindications:** Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

**Warnings:** Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

*Use in Pregnancy:* Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

**Precautions:** Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

**Adverse Reactions:** Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. Similar therapy is indicated for overdosage.

Lens opacities have been reported, and routine slit-lamp examinations should accompany prolonged use. Paradoxical increase in intraocular pressure may occur and be alleviated by a mydriatic.

**Dosage and Administration:** Initial titration and dosage adjustments must be individualized to obtain maximal therapeutic effect. Patient must be observed closely during initial period. If response is not adequate within first 24 hours, consider other measures. Keep frequency of use to a minimum in all patients, but especially in children.

Since technic is crucial to proper and safe administration, consult Direction Circular for full details.

**Supplied:** In 5-cc OCUMETER® Ophthalmic Dispenser containing 0.125 or 0.25 percent solution and sodium chloride; benzalkonium chloride 1:5000 added as preservative.

*For more detailed information, consult your MSD representative or see the Direction Circular. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

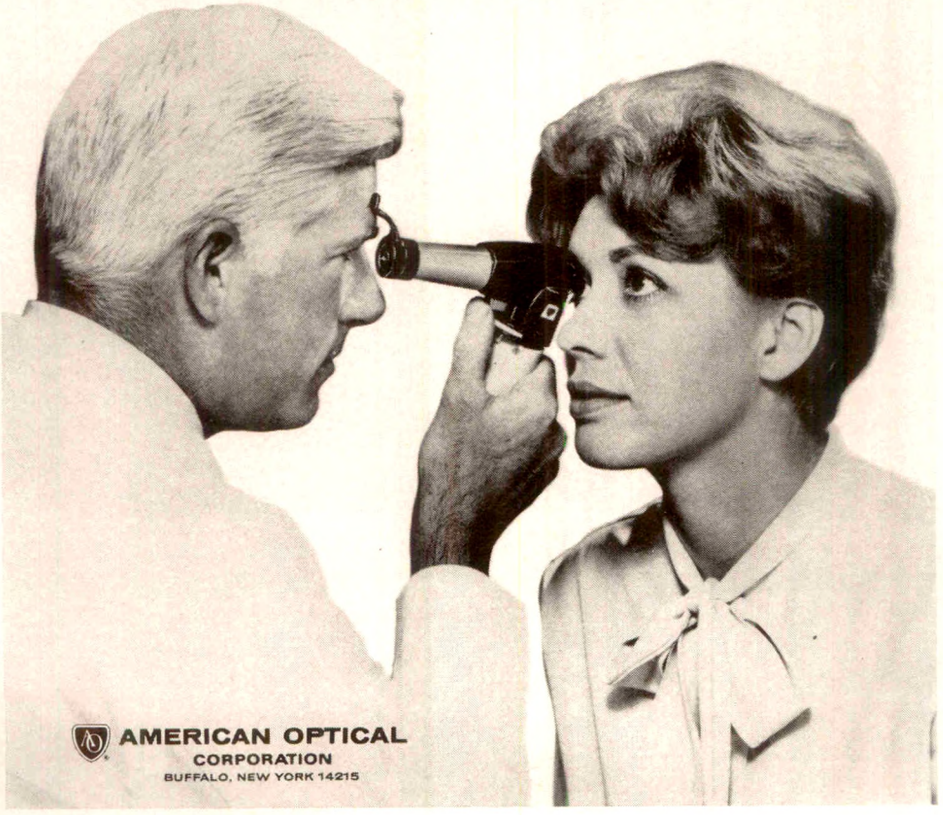
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# Now, an indirect ophthalmoscope with an erect image, ideal for routine examination.



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# CONTACT LENSES AND THE APHAKIC PATIENT

## Part 1: Factors in Lens Selection

The important advantages of contact lenses over spectacles, for aphakics, are well understood: greater field of view, elimination of aberrations, reduced magnification and major cosmetic improvement. To gain these benefits, the patient is willing to tolerate considerable discomfort and visual disturbance. The apparent successes achieved with such highly motivated patients have misled some practitioners into thinking that aphakics are the easiest to fit of all contact lens wearers.

In fact, however, proper fitting of the aphakic eye is a highly complex matter, because of: (1) Tendency of high-plus lenses to ride down and be moved excessively by the lids, due to their greater thickness and weight and their more forward center of gravity; (2) Often flaccid or low lower lids of older patients, unable to support the weight of some low-riding lenses, may allow them to dig into and irritate the lower limbus; (3) Pupillary irregularities, such as keyhole or upward-displaced pupils, which are still quite common; and (4) High degree of corneal cylinder 'against the rule' often found after cataract surgery.

To avoid visual disturbances such as flare, ghost images or double vision, it is imperative to position the contact lens *so that the optical zone covers the entire exposed pupil at all times*. Proper choice from among the following three corneal lens constructions will help the practitioner to achieve the desired lens positioning:

(1) MINUS-CARRIER LENTICULAR LENS
(2) TP (TANGENTIAL PERIPHERY) LENS
(3) SINGLE-CUT LENS

The correct selection depends on the pupil and lid characteristics of each individual case. For example: keyhole pupils require lenses which ride somewhat above center, to completely cover the exposed pupil, unless the upper lid extends down far enough to cover virtually all of the iridectomy, *making the exposed pupil almost round*. Larger pupils require lenses with larger optical zones, as do lenses which tend to be displaced laterally because of 'against the rule' astigmatism or decentered corneal apical caps. For flaccid lower lids, thick lens edges are deliberately constructed to better support the weight of low-riding lenses; or, the lenses may be designed to ride up, held there by the upper lids. With tight upper lids, lenses least affected by upper lid pressures are needed. The practitioner must consider all these factors: upper and lower lid position and tension, and size, shape and position of the pupils.

STANLEY GORDON, *President*

*(to be continued)*

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## EDT-103

A new dimension in the detection and management of glaucoma—

Surgical Products Division, Alcon Laboratories, Inc./ P.O. Box 1959, Fort Worth, Texas 76101

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**Caution:** Federal law prohibits dispensing without prescription.

**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902

t's a lousy feeling
ake up in the morn
with your eyelids
stuck together.

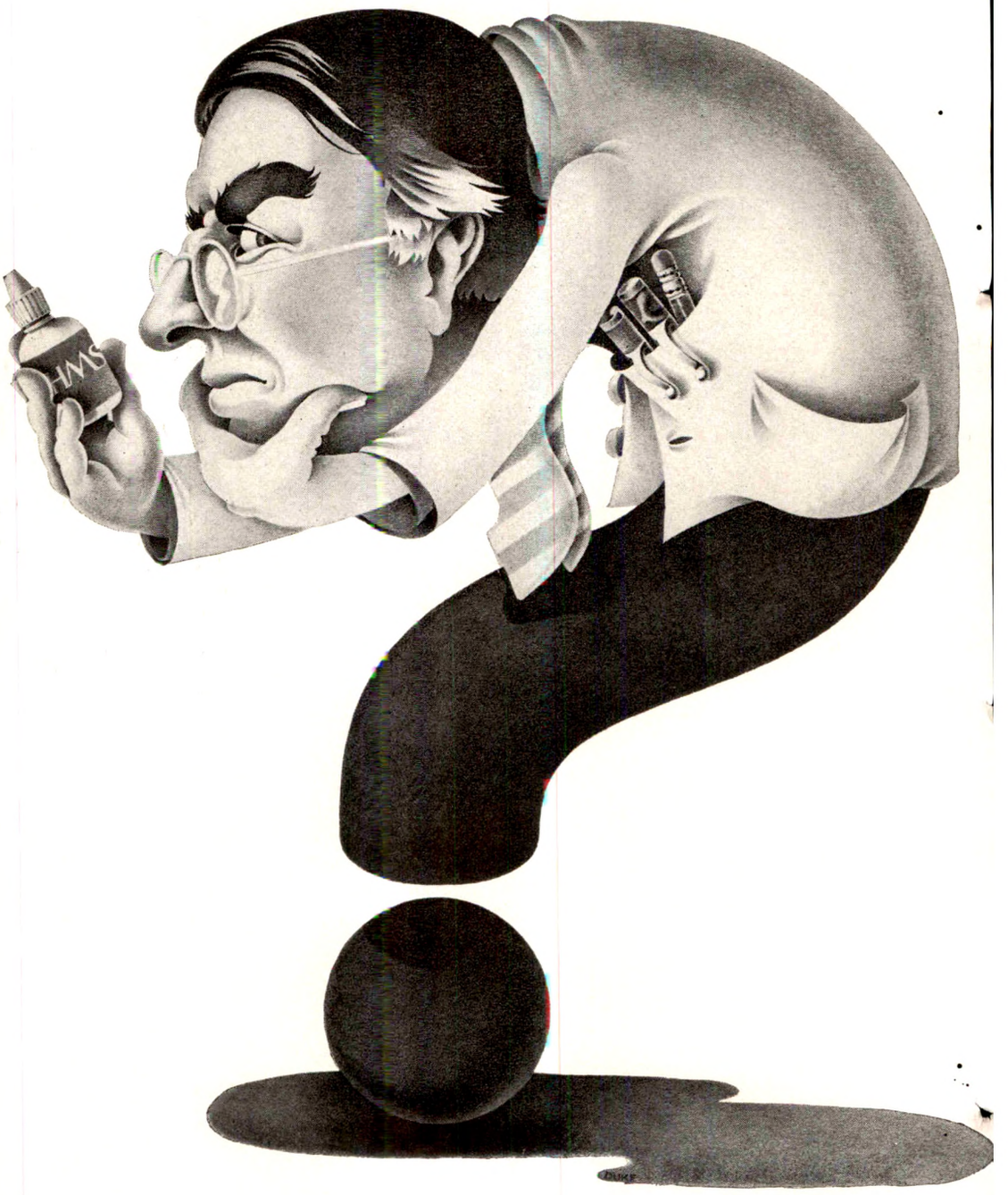


o medication residue with Vasocidin
othing to wash away in the morning
's an antibacterial, steroid, decon-
estant combination in true solution
Vorks fast because it disperses fast
elps relieve nonpurulent blepharitis
nd conjunctivitis more effectively
tarts the day right.

Vasocidin
clear solution that isn't sticky

# LAST YEAR W TOLD Y-U AB-UT TH "PRESSURE-SPARING" EFFECT OF HMS...

(medrysone)



# ...APPARENTLY YOU WANT TO KNOW MORE.

# SO TAKE THIS NEW LOOK AT HMS.

Drawing on nearly seven years of extensive clinical research experience, let's consider those questions you have asked most frequently.

### "Is HMS too mild to benefit my patients with inflammatory conditions?"

In the past five years, numerous independent studies on HMS (medrysone) have been published including those by Becker, and Thygeson.[1-4] Virtually all have reached the same conclusions: HMS is an effective treatment for superficial ocular inflammations.

Additionally, in a recent survey, 76% of the ophthalmologists interviewed who had tried HMS, found it effective when used for the recommended conditions.[5]

### "What therapeutic possibilities are now open to me, with HMS, that were not available with other mild steroids?"

First, over 30% of the population is likely to respond to steroids with an intermediate to high increase in intraocular pressure; steroid use with these patients must therefore be selective and cautious.[6] With HMS, most of these patients now can safely receive long-term steroid treatment.

Secondly, there are those glaucoma patients who must be treated specifically with epinephrine but are nevertheless sensitive to this drug. With HMS as concomitant therapy, Becker and Kolker reported that there was "sufficient improvement in glaucoma control so as to avoid surgery" by allowing continuation of epinephrine therapy.[7]

### "I haven't seen a rise in IOP with mild steroids. Isn't the real concern with the more potent steroids?"

There is ample evidence that .1% dexamethasone produces significant increases in IOP[1,4,8], and even .12% prednisolone, the mildest of the commercially available ophthalmic steroids, has the potential to increase IOP. Conversely, Doctors Becker and Kolker found in their investigational study that "medrysone (HMS) can be administered to patients four times a day for periods of several months with essentially no elevation of intraocular pressure even in individuals highly susceptible to such elevation."[7]

### "Can I treat uveitis and iritis with HMS?"

It is *not* indicated for these conditions. Its merits should only be judged in those conditions where indicated: allergic and vernal conjunctivitis, episcleritis, and epinephrine sensitivity.

### "Is HMS uncomfortable for the patient to use?"

Results of a recent patient study showed that 96% of those tested found HMS completely comfortable in the eye.[9] Though early batches of the product did cause some minor irritation to the eyes of a few patients, this has not been a recurring problem.

HMS® (medrysone)
LIQUIFILM® OPHTHALMIC SUSPENSION

ALLERGAN

Please see next page for Prescribing Information.

Prescribing Information for

# HMS® (medrysone)

LIQUIFILM® OPHTHALMIC SUSPENSION

DESCRIPTION: Contains:
medrysone.....1.0%
Liquifilm® (polyvinyl alcohol).....1.4%
with: benzalkonium chloride, disodium edetate, sodium chloride, potassium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, methylcellulose, purified water, and sodium hydroxide or hydrochloric acid if needed to adjust pH. HMS (medrysone) is related structurally more to progesterone than to other available corticosteroids.

INDICATIONS: HMS (medrysone) is effective in the treatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis and epinephrine sensitivity. HMS (medrysone) is not indicated in iritis or uveitis as its therapeutic effectiveness has not been demonstrated.

CONTRAINDICATIONS:
HMS (medrysone) is contraindicated in the following conditions:

1. Acute untreated purulent ocular infections.
2. Acute herpes simplex (dendritic) keratitis.
3. Viral diseases of the conjunctiva and cornea.
4. Ocular tuberculosis.
5. Fungal diseases of the eye.
6. Hypersensitivity to any of the components of the drug.

WARNINGS:

1. Infectious diseases of the eye may be masked, enhanced or activated by steroids.
2. Corneal or scleral perforation occasionally has been reported with prolonged use of topical steroids. In high dosage they have been associated with corneal thinning.
3. Prolonged use of topical steroids may increase intraocular pressure although data from 2 uncontrolled studies[4,5] indicate that in patients with increased intraocular pressure and in those susceptible to a rise in intraocular pressure upon application of topical steroids, there is less effect on pressure with HMS than with dexamethasone or betamethasone.
4. Prolonged use of topical corticosteroids may rarely be associated with development of posterior subcapsular cataracts.
5. Systemic absorption and systemic side effects may result with the use of topical steroids.

PRECAUTIONS:

1. HMS (medrysone) is not recommended for use in iritis and uveitis as its therapeutic effectiveness has not been demonstrated in these conditions.
2. With prolonged use of HMS (medrysone) the intraocular pressure and lens should be examined periodically.
3. In persistent corneal ulceration where a steroid has been used, or is in use, fungal infection should be suspected.
4. The use of topical steroids in pregnancy should be limited to conditions serious enough to warrant such treatment, so that possible risk to the fetus may be justified by the expected benefit to the mother.

ADVERSE REACTIONS: Occasional transient stinging and burning may occur on instillation.

DOSAGE AND ADMINISTRATION: One drop instilled in the conjunctival sac up to every four hours.

SUPPLY:
As a 5 cc. sterile suspension in plastic dropper bottles on prescription only.

NOTE: Bottles filled to one-half capacity for proper drop control. Do not freeze.

REFERENCES:


1. Drance, S.M. and Scott, S.: A Comparison of Actions of Dexamethasone and Medrysone on Human Intraocular Pressure. Canad. J. Ophth., 3:159, 1968.
2. Bedrossian, R. H., and Eriksen, S. P.: The Treatment of Ocular Inflammation with Medrysone, Arch. Ophth., 81:184, Feb., 1969.
3. Dorsch, W., and Thygeson, P.: The Clinical Efficacy of Medrysone, A New Ophthalmic Steroid, Amer. J. Ophth., 65:74, Jan. 1968.
4. Spaeth, G. L.: An Anti-Inflammatory Steroid Without Apparent Effect on Intra-Ocular Pressure, Arch. Ophth., 75:783, 1966.
5. Data on file, Allergan Marketing Department.
6. Armaly, M. F.: Factors Affecting the Dose Response Relationship in Steroid-Induced Ocular Hypertension, Chapter VII, Ocular Anti-Inflammatory Therapy, Ed. by H. E. Kaufman, Charles C. Thomas, Springfield, Ill., 1970, pp. 88-97.
7. Becker, B., and Kolker, A. E.: Intraocular Pressure Response to Topical Corticosteroids, Chapter 9, Ocular Therapy, Complications and Management, Ed. by I. H. Leopold, The C. V. Mosby Co., St. Louis, 1967, pp. 79-83.
8. Nelson, E. L., Ophthalmic Steroids, Chapter XVII, Ocular Anti-Inflammatory Therapy, Ed. by H. E. Kaufman, Charles C. Thomas, Springfield, Ill., 1970, pp. 217-23.
9. Data on file, Allergan Research Department.


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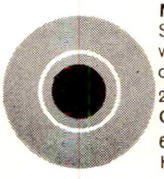
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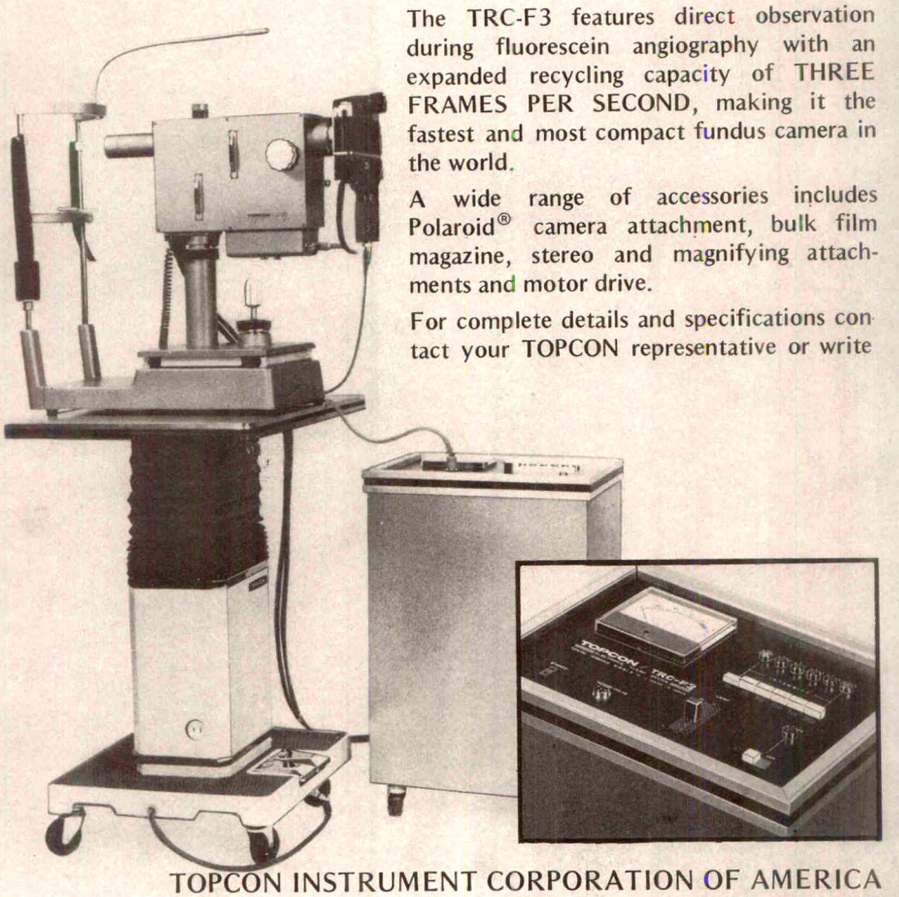
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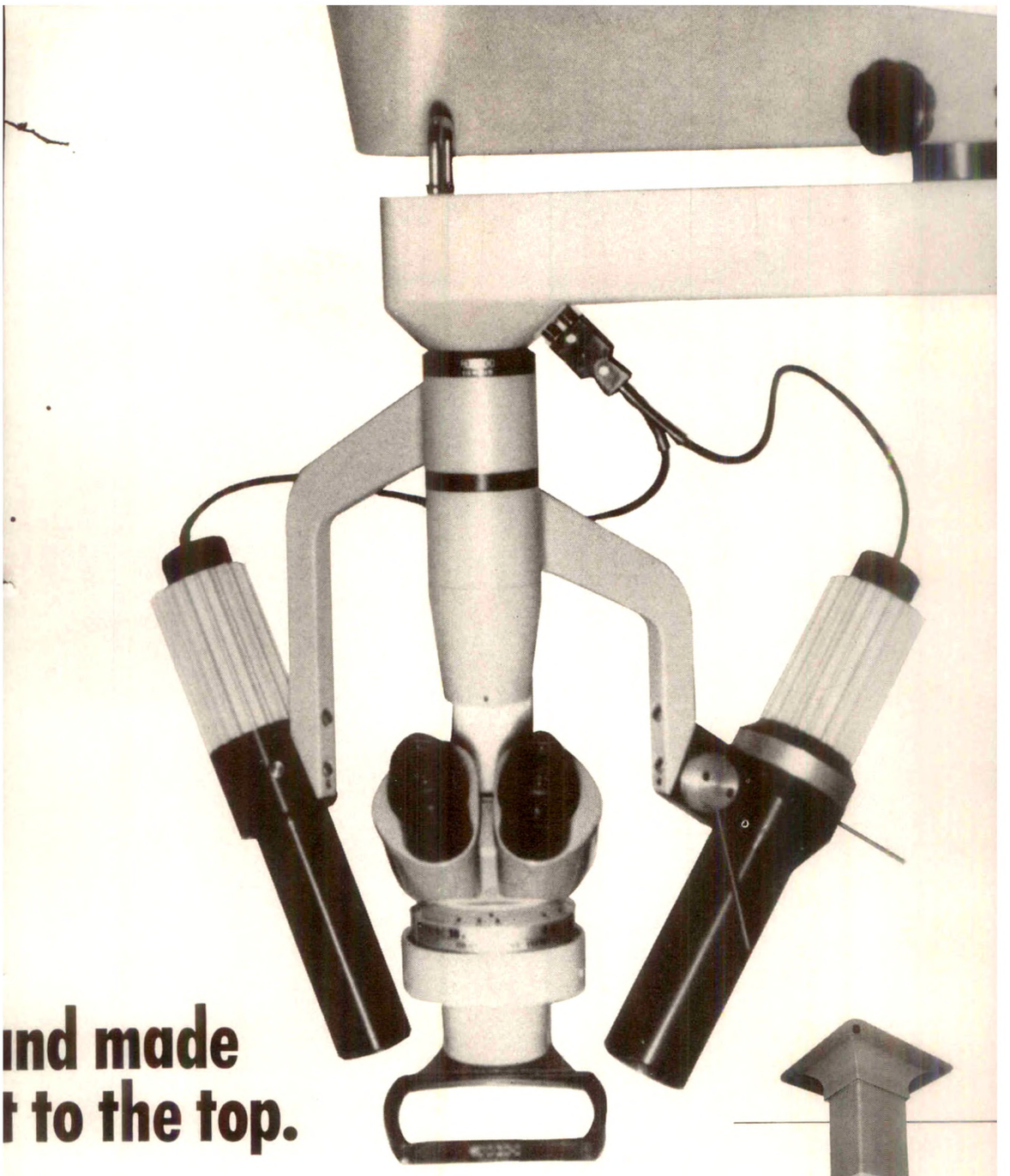
# We started at the bottom..

**Troutman Ophthalmic microscopes now com in floor *and* ceiling mounted units.**

A floor and ceiling mounted microscope t fit all the required needs of the Ophthalmi surgeon.

The ceiling mounted microscope has a mem ory system that virtually repositions it to th exact focal distance. In addition it moves hori zontally on a motorized ceiling track. This per mits the operating room to be used for othe than ophthalmic surgery.

Floor Model
Catalog No. 10-108

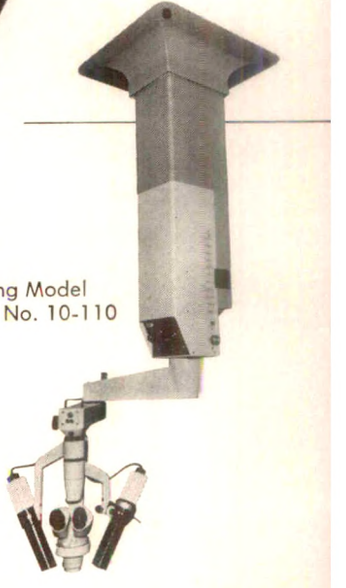


# ınd made
# t to the top.

The floor unit also moves easily on retractble, conductive casters, yet is absolutely stale during surgery. Both floor and ceiling units ave foot controlled zoom and focusing, and it illumination with scanning devices.

New Special Options available for both oor and ceiling units:

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Ceiling Model
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# sterile...
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The Ophthalmic Medication Delivery System
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Non-roll dropper unit

Easy grip for controlled drop

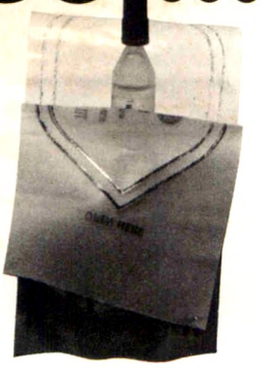
Color coded easy-to-open friction cap

Realistic quantity of medication for operative or post-operative use

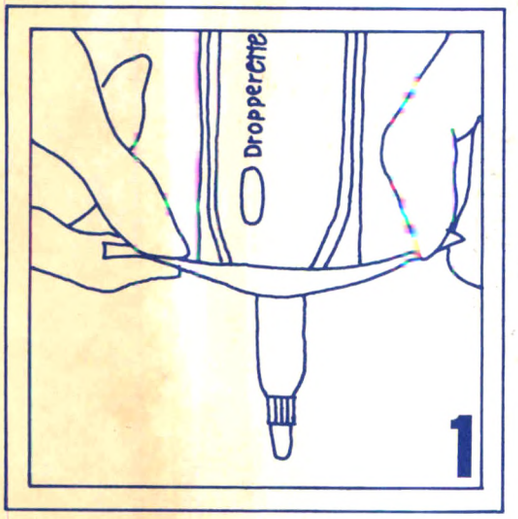

PILOMIOTIN 2%
(Pilocarpine HCl)

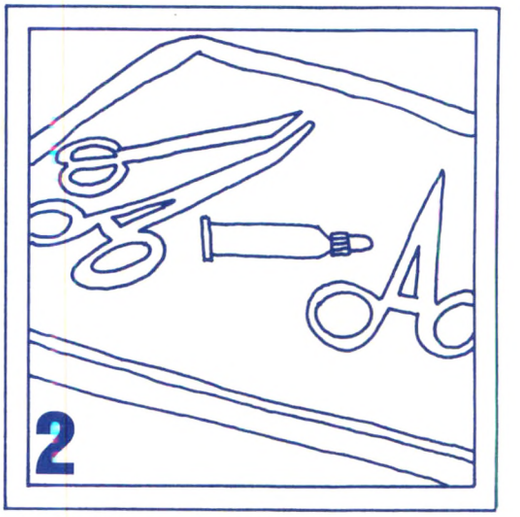
# Dropperettes®...

Sterile Pack



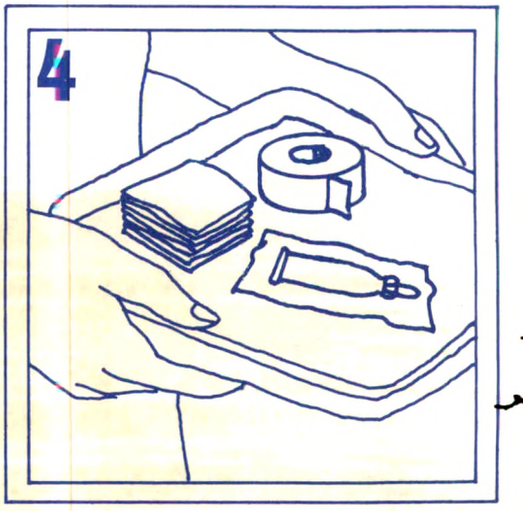
1. Easy-to-handle
2. No compromise in sterility
3. Easy to use during surgery
4. Ideal for post-operative use



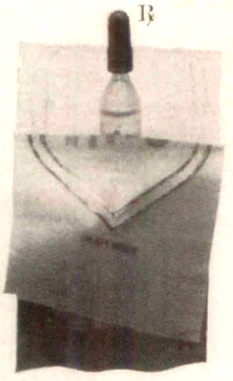

1 When the plastic envelope is peeled apart, a totally sterile DROPPERETTE is ready for delivery to the surgeon or to the instrument tray. Won't roll—flat end design. 2 The outer surface is sterile. Virtually no risk of package edge contamination or contamination of the surgical instrument tray. 3 Extended spout and controlled drop action for ease and accuracy of use. 4 Assures sterile medication delivery at the bedside.



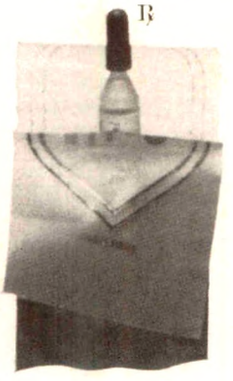



# Frequently Used Ophthalmic Medications . . . In the Most Convenient O.R. Delivery System

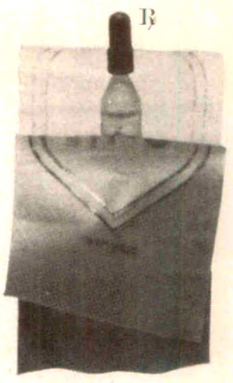
**ARGYROL® S.S. 20% (1 cc.)**



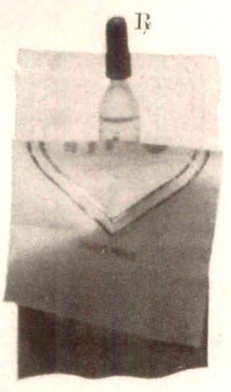
**ATROPISOL® (1 cc.)**
(Atropine Sulfate)
0.5% 1% 2%



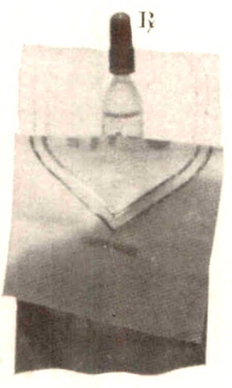
**EPINEPHRINE 1:1000 (1 cc.)**
(as the hydrochloride)



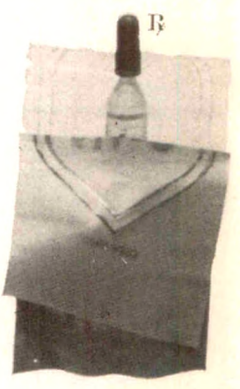
**FLUORESCEIN SODIUM 2% (1 cc.)**



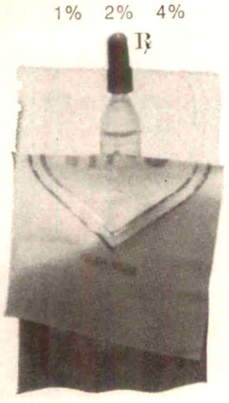
**HOMATROPINE HBr (1 cc.)**
2% 5%



**PHENYLEPHRINE HCl 10% (1 cc.)**



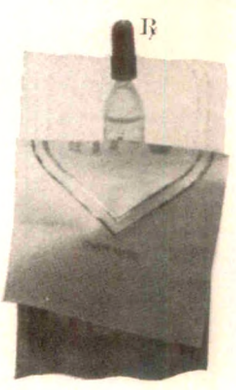
**PILOMIOTIN® (1 cc )**
(Pilocarpine HCl)
1% 2% 4%



**SULFACETAMIDE SODIUM 10% (1 cc.)**

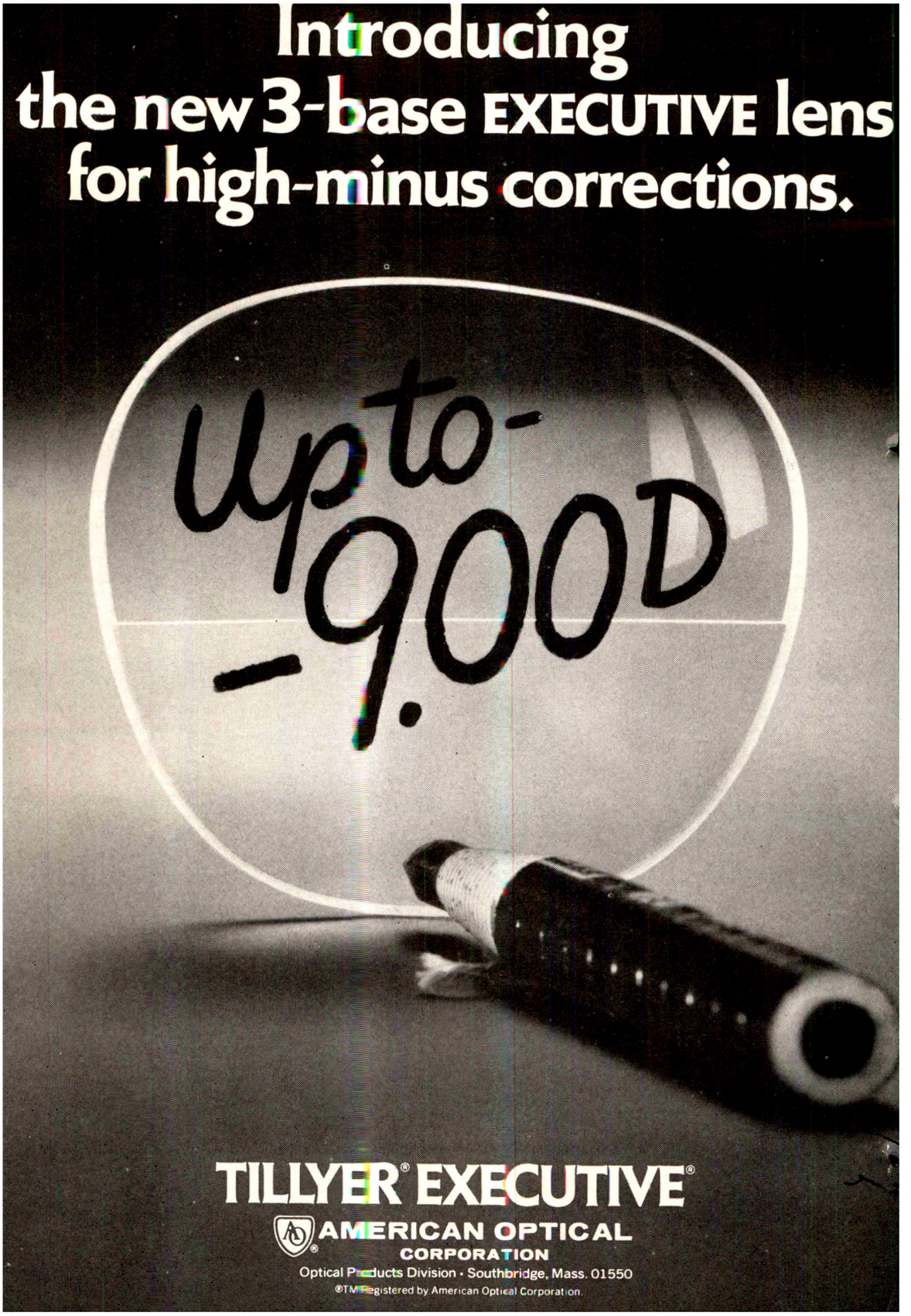


**TETRACAINE HCl 0.5% (1 cc.)**



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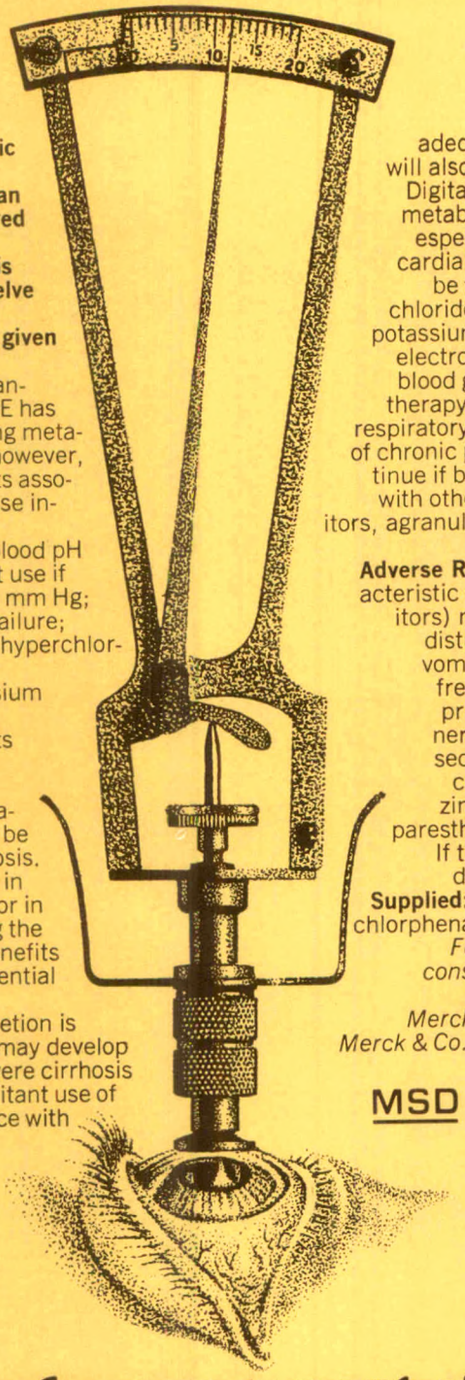

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**orally effective, potent carbonic anhydrase inhibitor**
**onset of action usually within an hour; maximal effect is observed in two to four hours**
**lowered intraocular pressure is often maintained for six to twelve hours**
**usually most successful when given in conjunction with miotics**
Compared to other carbonic anhydrase inhibitors, DARANIDE has a lesser propensity for causing metabolic acidosis. Please note, however, that this and other side effects associated with carbonic anhydrase inhibitors may occur.

**Contraindications:** To avoid blood pH decreases below 7.20, do not use if arterial $pCO_2$ greater than 63 mm Hg; hepatic insufficiency; renal failure; adrenocortical insufficiency; hyperchloremic acidosis; conditions in which sodium and/or potassium serum levels are depressed. Should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased to the point of narcosis.

**Warning:** Should not be used in women of child-bearing age or in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh potential adverse effects.

**Precautions:** Potassium excretion is increased and hypokalemia may develop with brisk diuresis, when severe cirrhosis is present, or during concomitant use of steroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Hypokalemia may be treated by use of potassium chloride or giving foods with a high potassium content. A close check on electrolyte balance, blood pH, and blood gases should be kept during therapy. Use with caution in severe respiratory acidosis or in the presence of chronic pulmonary infection; discontinue if blood pH falls below 7.20. As with other carbonic anhydrase inhibitors, agranulocytosis, thrombocytopenia, or renal calculi are possible.

**Adverse Reactions:** Side effects (characteristic of carbonic anhydrase inhibitors) may include gastrointestinal disturbances (anorexia, nausea, vomiting), constipation, urinary frequency, mild skin eruptions, pruritus, headache, weakness, nervousness, globus hystericus, sedation, lassitude, depression, confusion, disorientation, dizziness, ataxia, tremor, tinnitus, paresthesias of hands, feet, tongue. If they occur, reduce dosage or discontinue drug temporarily.

**Supplied:** Tablets containing 50 mg dichlorphenamide each, in bottles of 100.

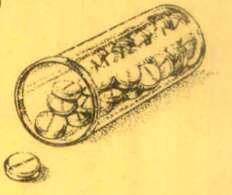
*For more detailed information, consult your MSD representative or see the Direction Circular.*

*Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

MSD MERCK SHARP & DOHME

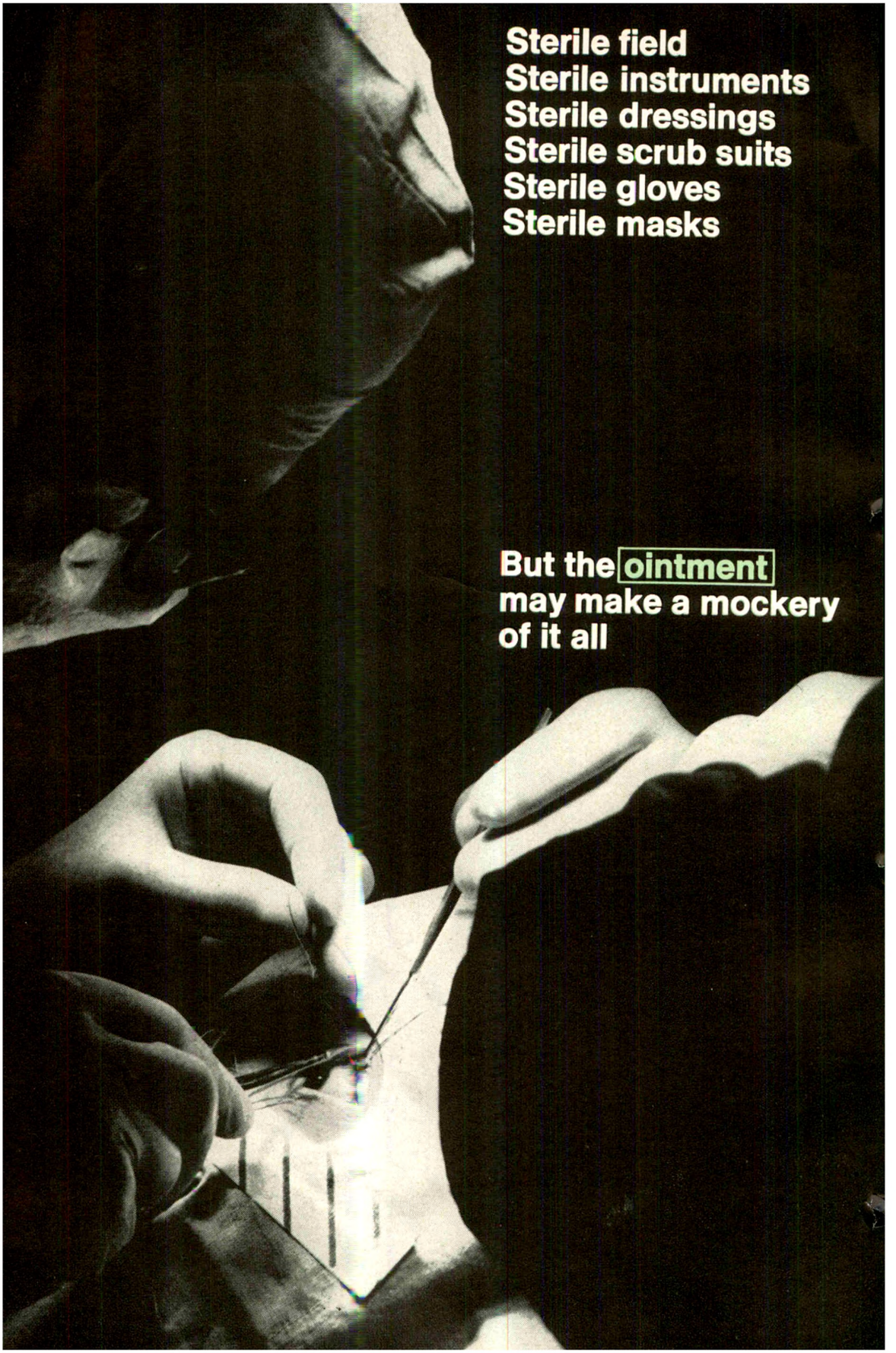
## ...in the oral management of glaucoma

# DARANIDE®



[DICHLORPHENAMIDE | MSD]

TABLETS, 50 mg


Sterile field
Sterile instruments
Sterile dressings
Sterile scrub suits
Sterile gloves
Sterile masks
But the ointment
may make a mockery
of it all

**"Iatrogenic infection must be seriously considered and eliminated by all concerned insofar as it may be prudently possible. [It] . . . may result in a break in sterile surgical technique . . . Those topical products for use in the environment of the hospital should be sterile. . . ."**
**—Evans, W. J.: FDA Papers, May 1970.**

**Vander Wyk and Granston[1] reported in 1958 that 71 out of 83 (85.5%) samples of ophthalmic ointments tested were unsterile. Other investigators, notably Bowman and Holdowsky[2], and Bowman[3] have also reported on ophthalmic ointment contamination using various testing methods.**

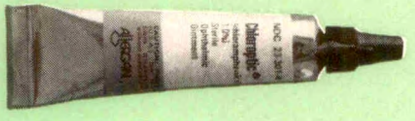


This plate was prepared from a commercially available ophthalmic ointment. The approximate number of microorganisms and the species (thereof per gram of ointment were:) Staphylococcus, 250; Achromobacter, 100; Nocardia, 50; Actinomyces, 50; Corynebacterium, 50; Bacillus, 200; Yeast, 50; Mold, 1900.



This plate shows the results obtained when one of a series of Allergan's new sterile ointments was tested using exactly the same procedure. No contamination could be detected.[4]

# Now, for the first time Allergan offers these New Sterile Ophthalmic Ointments.



## Chloroptic® (chloramphenicol)
### Sterile Ophthalmic Ointment
Contains: chloramphenicol . . . 1.0% (10mg/Gm) chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.



## Chloroptic™-P
### Sterile Ophthalmic Ointment
(chloramphenicol-prednisolone)
Contains: chloramphenicol . . . 1.0% (10mg/Gm) prednisolone alcohol 0.5% (5mg/Gm) chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.



## Atropine Sulfate 1.0%
### Sterile Ophthalmic Ointment
Contains: atropine sulfate . . . 1.0% with: chlorobutanol (chloral deriv. as a preservative) . . . 0.5% with: white petrolatum, mineral oil.

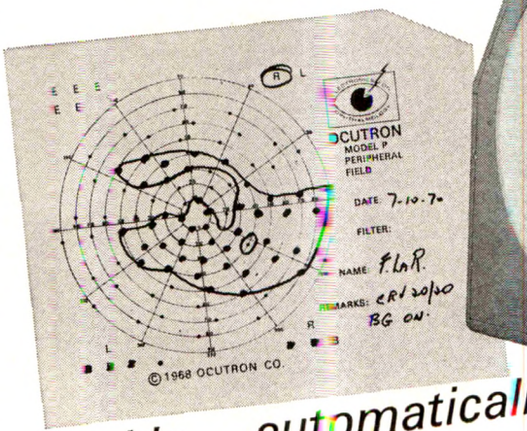

1. R. W. Vander Wyk and A. E. Granston, *J. Am. Pharm. Assoc., Sci. Ed.*, *47*, 193 (1958)
2. F. W. Bowman and S. Holdowsky, *ibid.*, *48*, 95 (1959)
3. F. W. Bowman, *J. Pharm. Sci., 58 (2):* 277 (Feb), 1969
4. Data from research files, Allergan Pharmaceuticals, Irvine, California


ALLERGAN Pharmaceuticals Irvine, California/Montreal, Canada

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## *offers you visual fields*

. . . whenever you want
. . . as often as you want
without your being there






*quickly . . . automatically!*

U.S. Patent Nos. 3,288,546
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Difficult and time-consuming fields like the above glaucoma field are as easily and quickly tested as a simple normal field.

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Particularly suitable for high volume performance. Simple enough for screening. Accurate enough for definitive, repeatable field study.

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***Check them:***

- ☐ Better view of macula with less reflection.
- ☐ Stereoscopic observation around opacities in the transparent media.
- ☐ Maximum stereopsis at all times commensurate with the size of the pupil.
- ☐ Now, after many years of research, one instrument[1] affords the best features for routine indirect ophthalmoscopy with the possibility of binocular viewing through pupils as small as 1.5 mm.
- ☐ Better illumination for viewing the fundus periphery.
- ☐ Adjustable diaphragms in the eyepieces insure easy and exact alignment of the ophthalmoscope both vertically and horizontally to prevent diplopia.
- ☐ A special optical system minimizes light loss and conducts most of the available light into the pupil.
- ☐ Built-in infrared filter prevents unnecessary heating of fundus tissues and makes examination far more comfortable for the patient.
- ☐ Eyepieces incorporating any lens corrections to suit the observer's prescription may easily be inserted and removed.
- ☐ Unusually large mirror attachment enables a second observer to view stereoscopically from either side of the primary observer.
- ☐ Headband is designed for comfort. Weight of the instrument is distributed over a large portion of any head to minimize the discomfort of wearing an instrument on the head for a prolonged period.
- ☐ All optical elements are completely enclosed and dust free.
- ☐ Lamp alignment knobs to focus filament are conveniently located outside the instruments.
- ☐ Intensity of illumination is continuously adjustable with a rheostat on the headband.
- ☐ Lamp housing is specifically designed to remain cool. Even after prolonged use it is not hot to the touch; there is a minimum of heat transmitted to the doctor's forehead.
- ☐ Filter is available for fluorescein study.

1. Designed by O. Pomerantzeff, D. Eng., C. L. Schepens, M.D. and others at the Retina Foundation, Boston.

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- ☐ Light Coagulator MF1000
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Name _____ Title _____
Hospital or Clinic _____
Address _____
City _____ State _____
Zip _____ Phone _____

**Composition:**

**Inflamase**

*Prednisolone Sodium Phosphate .....0.125%
(Equivalent to Prednisolone 0.1%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

**Inflamase Forte**

*Prednisolone Sodium Phosphate 1.0%
(Equivalent to Prednisolone 0.8%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

Prednisolone Sodium Phosphate is a water soluble inorganic ester of prednisolone. It is approximately 2,000 times as soluble in water at 25°C. as is hydrocortisone.

*Licensed under patent #3,134,718.

**Indications:** Inflamase and Inflamase Forte ophthalmic solutions may be used effectively in the following conditions of the anterior segment of the eye: superficial keratitis, including punctate epithelial lesions (Thygeson type), phlyctenular keratoconjunctivitis, and Sjogren's keratoconjunctivitis (with systemic steroids); deep keratitis, including interstitial or parenchymatous keratitis, acne rosacea, sclerosing keratitis; herpes zoster opthalmicus (do not use in herpes simplex); non-purulent conjunctivitis, including vernal, allergic, catarrhal; iridocyclitis; acute iritis; recurrent marginal ulceration, whether endogenous or due to atopic or contact allergies, or microbial allergy; corneal injuries, such as aseptic thermal, radiation, or chemical burns and corneal injuries following surgery or the penetration of foreign bodies; lid allergy; and non-purulent blepheritis, including catarrhal and allergic.

Inflamase and Inflamase Forte ophthalmic solutions have their principal effect on the anterior segment of the eye (cornea and the anterior uvea), with acute disorders responding more favorably than chronic disorders. Inflamase Forte 1% solution is recommended for moderate to severe inflammations particularly when rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

**Dosage:** Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops 2 to 4 times daily.

**Contraindications:** Contraindicated in acute herpes simplex, ocular tuberculosis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal diseases of the eye. Purulent conjunctivitis, purulent blepharitis, and infectious conditions are contraindications to the use of steroids.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

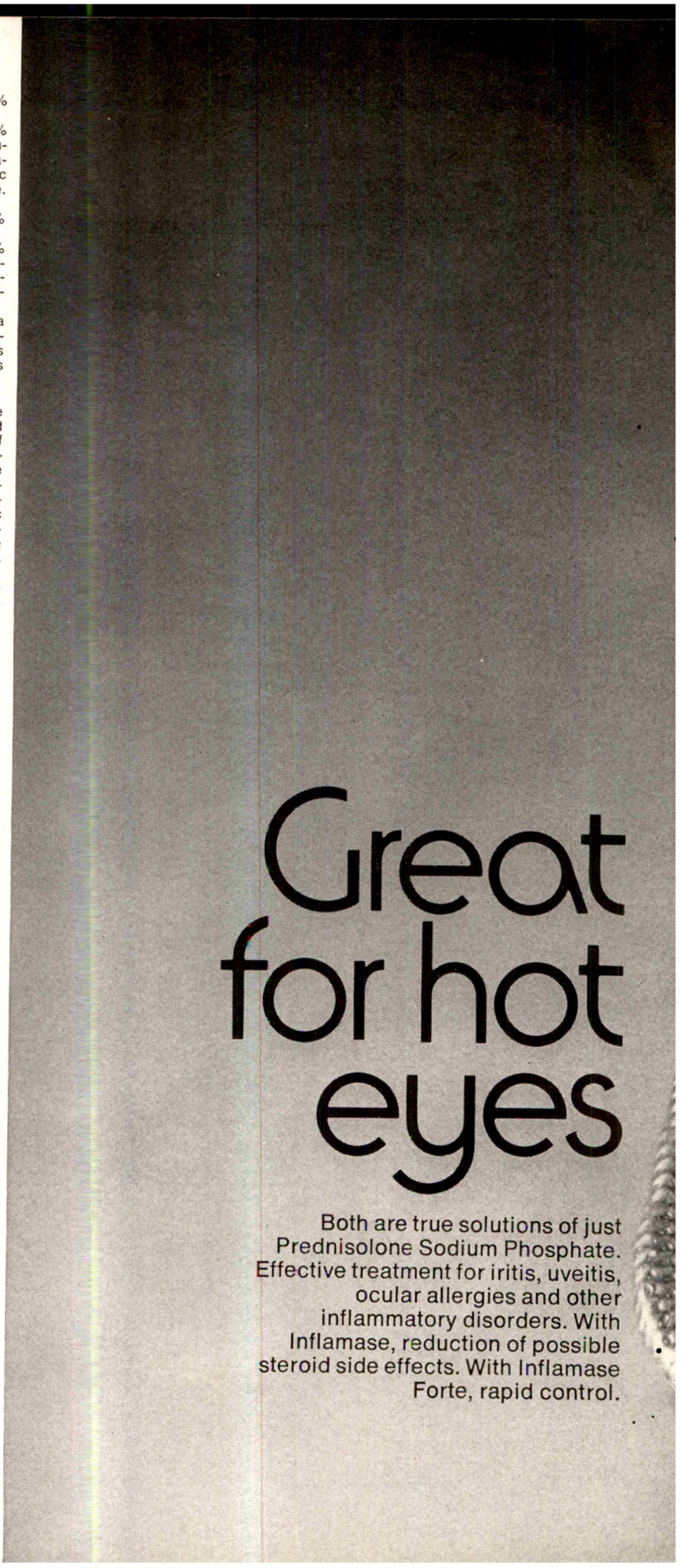
**Warning:** If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.

**How Supplied:** 5 cc plastic squeeze bottle with dropper tip. These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Store in cool place. Protect from light.

**Caution:** Federal law prohibits dispensing without prescription.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902



# Great for hot eyes

Both are true solutions of just Prednisolone Sodium Phosphate. Effective treatment for iritis, uveitis, ocular allergies and other inflammatory disorders. With Inflamase, reduction of possible steroid side effects. With Inflamase Forte, rapid control.




**Inflamase**
for most inflammations.

**Inflamase Forte**
for the tough ones.

**Zoom Optics**—A true zoom unit, the Nikon Slit Lamp Microscope has continuous variable power from 7x to 35x. And yet, the image remains precisely centered and in critical focus throughout the entire range of magnification.

**Simultaneous Photography**—With the Nikon Slit Lamp Photo Attachment, you can view critically and photographically record exactly what you see—at the moment you see it. It is not necessary to remove your examining eye from the microscope to focus or use the camera. If needed you can freeze eye motion completely by use of strobe light.

**Unique Controls**—The slit mechanism is precisely controlled by coaxial vertical and horizontal controls. You can continuously vary the size of the slit with either your right or left hand from one set of controls. And the degree of control is exceptional too. *Both* the width and length of the slit can be precisely adjusted to complete extinction.

**Versatility**—Designed primarily for office practice the Nikon Slit Lamp is equally at home in the research laboratory. Equipped with the teaching head it is highly suitable for the classroom too. And like all Nikon Ophthalmic Instruments, it is guaranteed for 10 years.

We believe that once you examine a Nikon Zoom Photo Slit Lamp Microscope, you'll be well on your way to having the instrument you've always wanted at half the price you thought you couldn't afford.

Write for 8 page detailed brochure or call for a demonstration. Nikon, Inc. Instrument Division Subs. of Ehrenreich Photo-Optical Industries, Inc. Garden City, N.Y. 11530. 516-248-5200. (In Canada: Anglophoto Ltd., Ont.)

EPI

# Now, Nikon brings you the slit lamp microscope you thought you couldn't afford.

New wide angle (45°) fundus camera, applanation tonometer and ophthalmoscope, can be seen in Booth 105-106 at the AAOO meeting, September 19-23, in Las Vegas.



Specific for
Herpes Simplex Keratitis

**STOXIL®**
**brand of IDOXURIDINE**

the only brand of IDU
available in two forms:
Solution—Ointment

Both now available in Canada




# The choice is yours

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

**Description: 'Stoxil' Ophthalmic Solution** contains idoxuridine (5-iodo-2'-deoxyuridine) **0.1% (1 mg./cc.)** in distilled water. Preserved with thimerosal, 1:50,000. **'Stoxil' Ophthalmic Ointment** contains idoxuridine **0.5% (5 mg./Gm.)** in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

**Contraindications:** Contraindicated in patients with known or suspected hypersensitivity to any of its components.

**Precautions:** Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of the therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

**Adverse Reactions:** Occasionally, irritation, pain, pruritus, inflammation, edema of eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

**How Supplied:** 0.1% Ophthalmic Solution (1 mg./cc.), in 15 cc. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./Gm.) in 4 Gm. tubes.

**Stability:** The Ophthalmic Solution should be stored in refrigerator until dispensed. 'Stoxil' Ophthalmic Ointment does not require refrigeration.

SK&F Smith Kline & French Laboratories

# !!! AQUALENS T.M !!!

*The All-New Years-ahead Hydrophilic Hard Contact Lens Adds a whole New Dimension to Contact Lenses*

**Developed By and Offered *Exclusively* By MORGAN OPTICS**

## NOW... and NEW...

FOR THE CONTACT LENS WEARER:

- **GREATER COMFORT**
- **LONGER WEARING TIME**
- **INCREASED WETTABILITY**
- **EASIER INSERTION AND REMOVAL**

Developed and tested by Morgan Optics, Dallas, Texas, the hydrophilic hard contact AquaLens, is now available for the greater comfort and wearing time of all who can wear ordinary hard contact lenses . . . **IN COLORS** *as well as clear!*

**Plus, AquaLens now makes contact-lens wear possible for many who previously could not tolerate contact lenses.**

Morgan Optics created AquaLens by changing the molecular structure of methylmethacrylate so that it is now hydrophilic (throughout the entire lens) rather than hydrophobic, and its angle of wettability is in the range of 25 to 30 degrees, in contrast to the 60 or 65-degree wettability angle of ordinary hydrophobic hard contact lenses.

AquaLens plastic has less surface tension than the ordinary hydrophobic hard contact lens, thus allowing tear-flow to adhere more uniformly to the new lens . . . giving greater comfort and longer wearing time.

AquaLens is prescribed and fitted in the same way as hydrophobic hard contact lenses, requires only the normal care and storage prescribed for other hard contact lenses, and is available in colors as well as clear.

AQUALENS *the new hydrophilic hard contact lens, is available ONLY from MORGAN OPTICS, INC.*

FOR ORDERING AQUALENS, OR FOR FURTHER INFORMATION, USE OUR FREE NATIONAL WATS LINE: 1-800-527-6314 OR MAIL IN THE COUPON.

**MORGAN OPTICS, INC**
**P. O. Box 806**
**Dallas, Texas 75221**
**214/748-9061**

TO: MORGAN OPTICS, INC.
P.O. Box 806
Dallas, Texas 75221

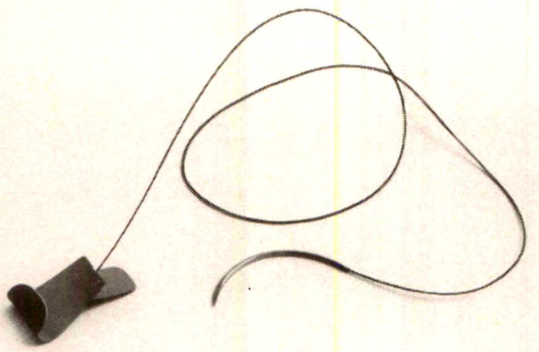
YES, I AM INTERESTED IN YOUR ALL-NEW AQUALENS

☐ Please send me full information!

Name _____

Address _____

City _____ Zip Code _____



This iris retractor doesn't tremble, doesn't tire, and doesn't stand in your way.

But it does move if the eye moves, because it is sutured directly to the sclera. Much less chance of trauma than with a hand-held retractor. The *Mentor*™ Iris-Clip, attached to a 4-inch suture and a *Micro-Point** needle, is packaged sterile and ready to use. Successful in over 1000 cataract extractions. Mentor Division, Codman & Shurtleff, Inc., Randolph, Mass. 02368.

Codman Mentor DIVISION

© 1970 by Codman & Shurtleff, Inc. *Micro-Point is a trademark of Ethicon, Inc.

# MORE THAN JUST A NEW NAME . . .

## UNIVERSAL OPHTHALMIC LABORATORIES, INC.

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A southwestern organization ready to serve you, wherever you are, whatever your needs are . . .

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All the major names in instruments and accessories, backed by an excellent service

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Manufacturers of UNIKAT, temporary cataract glasses, and the world renown WAFER PRISM

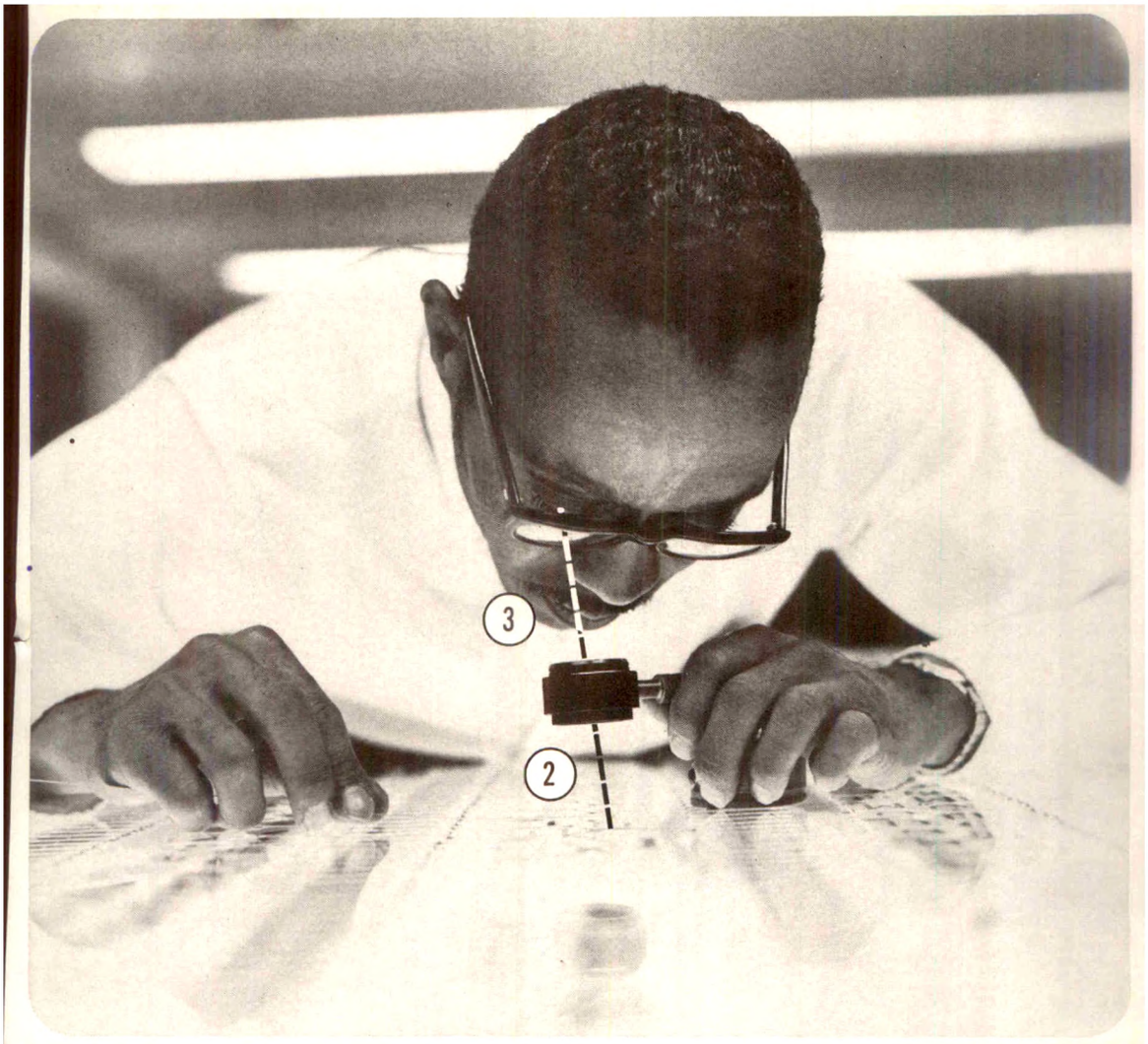
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Complete, modern production facilities enables us to offer you the best lenses and the best service on all your contact lens needs

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*Occupational vision studies*
*(From Study #21, Volume II, Guide to Occupational and Other Visual Needs)*

# Draftsman

In making a space capsule or an electric iron, a nuclear submarine or a TV set, a bridge or a typewriter, intricate detailed plans are needed to guide the people who make the object. These plans are carefully and painstakingly drafted by a technician called a "draftsman".

Working as he does with complicated figures and drawings on a large drafting table, it is needless to point out that the draftsman requires critical vision at many distances and from many angles.

When that draftsman reaches the presbyopic stage, the help he will need to see clearly for his work is available from the more than thirty-two different styles and sizes of multifocals manufactured by The Vision-Ease Corporation. Just check your lab or refer to the Vision-Ease Product Handbook, a copy of which can be obtained for the asking.

VISION-EASE®

THE VISION-EASE CORPORATION
St. Cloud, Minnesota 56301

***Vision-Ease has a one-quality line . . . the finest.***
***This is what your patient gets when you specify Vision-Ease***

# We're not satisfied with just being first.

**Our researchers are still creating more firsts for your contact lens patients.**




**CLENS™** *The first cleaning solution* specifically designed for use by the patient. Rinses rapidly from the lens, removing films and deposits by its thorough cleansing action.

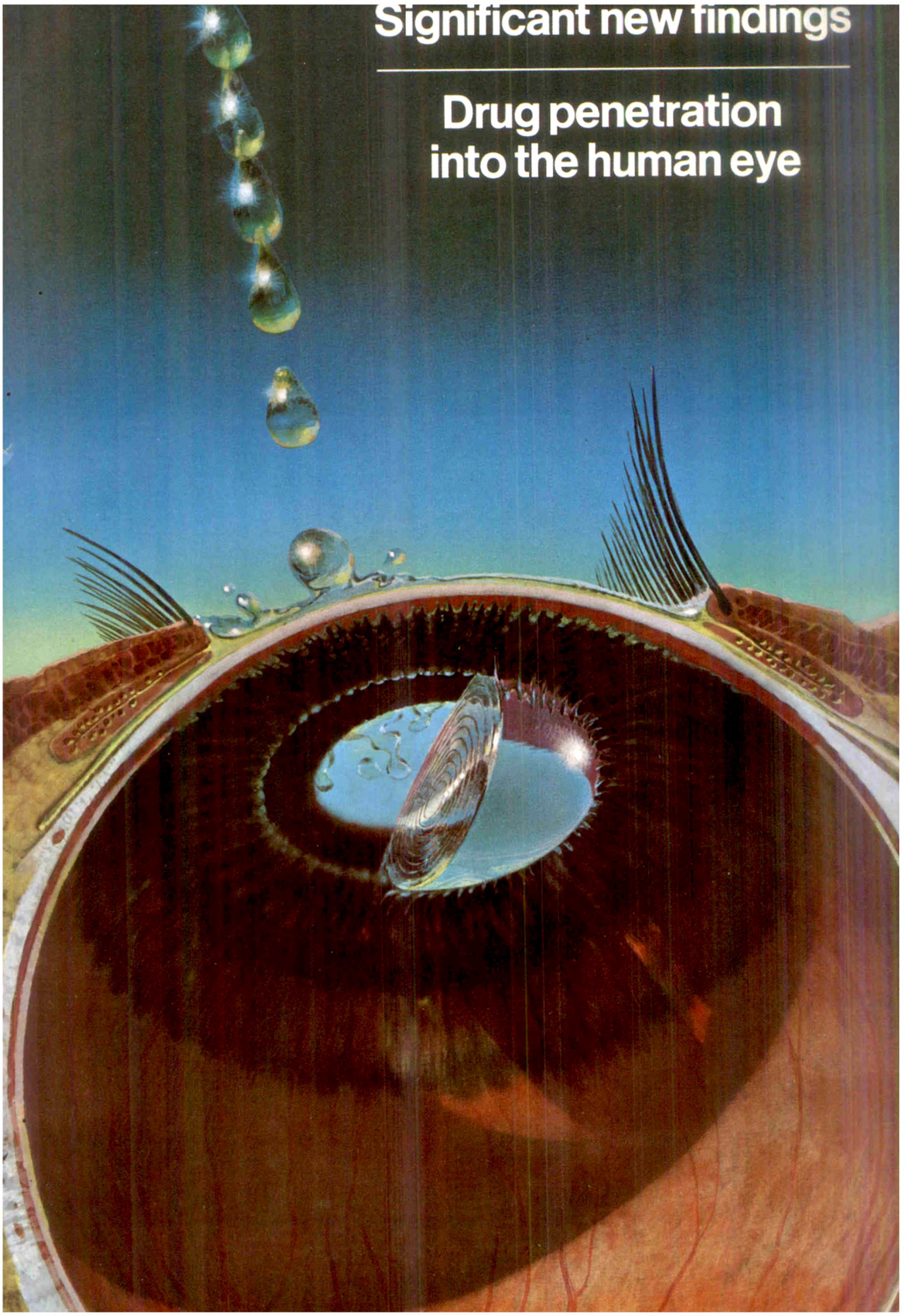
**SOACLENS™** *The first combination soaking-wetting solution* adjusted to the proper pH, eliminates necessity for application of separate wetting solution, and allows insertion of lens directly from a Soaclens bath.

**ADAPT™** *The first cushioning solution.* Effectively reduces lens sensation and over-awareness. Ideal during adaptation and for chronic problem cases. Helpful, too, in providing extra comfort for well-adapted wearers.

*Write for literature and clinical samples:*

**Burton, Parsons & Company, Inc.** *Manufacturers of Ethical Pharmaceuticals Since 1885*

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Significant new findings
Drug penetration
into the human eye

# for the first time independent research relates ocular drug penetration in humans to your choice of ophthalmic vehicles

## Proof of penetration—new fluorophotometry concentration/duration study[1]

Using a slit lamp fluorophotometer, "the effects of ophthalmic vehicles on the intraocular penetration of topical fluorescein in man" were determined. "Quantitative data on ocular penetration of this drug, in man, in vivo are presented."

### The study

Fluorescein combined with hydroxypropyl methylcellulose 0.5%, polyvinyl alcohol 1.4% and aqueous; each vehicle instilled in the eyes of 20 normal subjects; each subject served as his own control; hourly measurements of attained drug concentration were made quantitatively using a slit lamp fluorophotometer.

### The findings

CORNEA

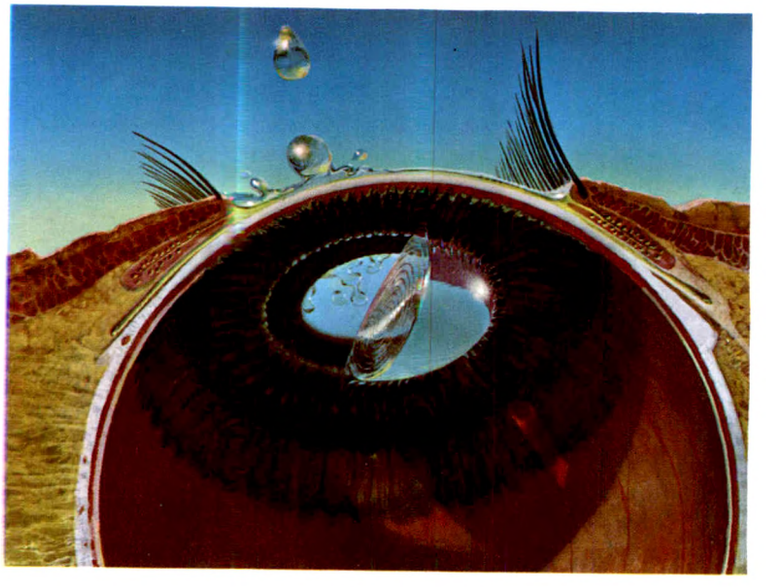
Over a three hour period, hydroxypropyl methylcellulose produced corneal drug levels 85% higher than polyvinyl alcohol and 43% higher than the aqueous vehicles.‡

AQUEOUS HUMOR

Over a three hour period, hydroxypropyl methylcellulose produced aqueous humor drug levels 93% higher than polyvinyl alcohol and 42% higher than the aqueous vehicle.‡‡

### The authentication

The authors state that their findings may, or may not, be true for drugs other than fluorescein. However, the findings reported above were achieved "consistently and reproducibly"; data were analyzed and tested for significance on a computer.



# when infectious inflammations demand a long-lasting sulfa/steroid

The Isopto® Cetapred vehicle makes for greater concentrations[1] of drug in ocular tissue. Combined with broad, anti-infective range, the high levels of anti-inflammatory action provide rapid and prolonged relief of symptoms—pain/hyperemia/exudation—greater therapeutic efficacy, and maximum patient comfort.

**Cetapred® Ophthalmic Preparations:**

**Description:** *Solution:* Sterile, containing: *Active:* Sodium Sulfacetamide 10%, Prednisolone Acetate 0.25%; *Vehicle:* Hydroxypropyl Methylcellulose 0.5%; *Preservatives:* Thimerosal 0.01%, Sodium Thiosulfate 0.1%; *Inactive:* Sodium Biphosphate, Dried Sodium Phosphate, Hydrochloric Acid (to adjust pH), Purified Water.

**Ointment:** Sterile, containing: *Active:* Sodium Sulfacetamide 10%, Prednisolone Acetate 0.25%; *Preservatives:* Methylparaben 0.05%, Propylparaben 0.01% *Inactive:* White Petrolatum, Anhydrous Liquid Lanolin, Mineral Oil.

**Precautions—Adverse Reactions:** Extended use may cause increased intraocular pressure, which should be checked frequently. Perforation may occur in diseases causing thinning of the cornea. Institute other therapy if favorable response is not obtained within reasonable period. Discontinue if sensitivity occurs.

**Contraindications:** tuberculosis, fungal, and most viral lesions of the eye; vaccinia; varicella; acute purulent conjunctivitis, acute purulant blepharitis.

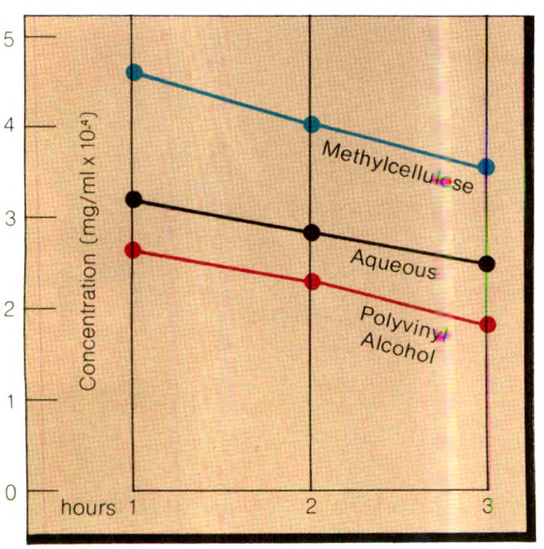
**Supplied:** In 5 cc and 15 cc Drop-Tainer® dispensers; sterile ointment in 1/8 oz. tubes.

**References: 1.** Waltman, S.R. and Patrowicz, T.C.: Invest. Ophthal. 9:966, 1970.
**2.** Linn, M.L. and Jones, L.T.: Amer. J. Ophthal. 65:76, 1968.

Isopto® vehicle (hydroxypropyl methylcellulose 0.5%)
produced significantly higher drug penetration and concentration
compared with 1.4% polyvinyl alcohol or aqueous vehicles.

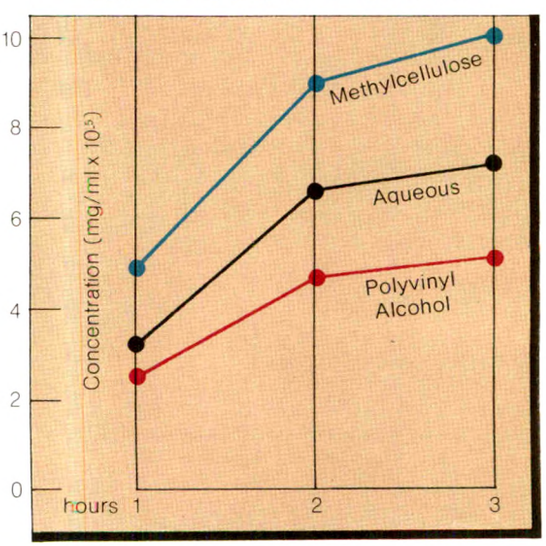
‡Concentration in human cornea

Corneal fluorescein concentration after topical 2% fluorescein in various vehicles.




‡‡Concentration in human aqueous humor

Aqueous humor fluorescein concentration after topical 2% fluorescein in various vehicles.

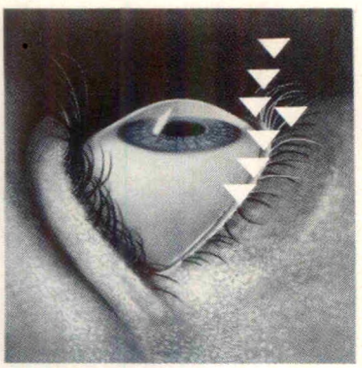



Adapted from Waltman, S.R. and Patrowicz, T.C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man, Invest. Ophthal. 9:966, 1970.

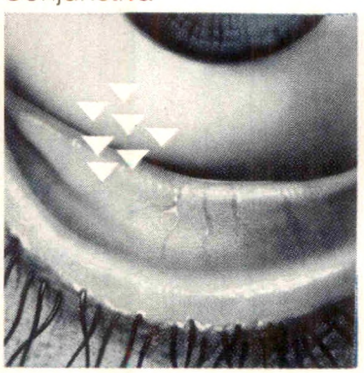
...therefore, when penetration makes the clinical difference

# long-lasting activity at these demand sites:

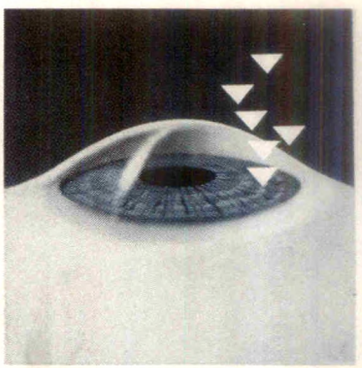
Lid



Conjunctiva



Cornea



**because Isopto®, the ideal ophthalmic vehicle, has 'staying power'**

extended surface coverage (over *cornea, conjunctiva, lids*)

extended contact time—resists drug washout[2]

extended activity and corneal penetration

Alcon

# ISOPTO® CETAPRED

sodium sulfacetamide 10%; prednisolone acetate* 0.25%;
vehicle: hydroxypropyl methylcellulose 0.5%

Penetrates into cornea and conjunctiva...
and stays there longer

and for uninterrupted therapy...at night, add
*sterile* Cetapred® Ointment

*Licensed under U.S. Patent 3,134,718


Nancy's classmates won't call her names now...



## and her accommodative esotropia no longer affects her grades

Over two years ago, Nancy showed an esophoria of 6 Δ at distance and an intermittent esotropia of 15 Δ at near, with imperfect fusion. She was put on PHOSPHOLINE IODIDE 0.125% O.U., at first once a day. This dosage regimen was reduced gradually to once a week. Orthoptic measures were employed to increase binocular control. Nancy now has an esophoria of 12 Δ at near, no tropia, and excellent stereopsis. Fusion is still variable for near. Vision is 20/20 in each eye. She no longer requires eyedrops.*

## for diagnosis

One drop of PHOSPHOLINE IODIDE 0.125% instilled in both eyes for two or three weeks can help determine if there is an accommodative basis for the esotropia.

## in treatment

If there is a significant accommodative factor present, the continued use of PHOSPHOLINE IODIDE alone is often sufficient for treatment.

If surgery is necessary, postoperative use of PHOSPHOLINE IODIDE may help correct a residual deviation.

*Case history courtesy of Orthoptic Clinic, Department of Ophthalmology, N.Y.U. Medical Center, N.Y. School of Medicine, New York, N.Y. Other children are professional models.

**BRIEF SUMMARY**
**(For full prescribing information, see package circular.)**

**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, browache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local):* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have also been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic):* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

**The Ophthalmos Division**
**AYERST LABORATORIES**
**New York, N.Y. 10017**

7121

in the management of accommodative esotropia

# Phospholine Iodide®

## (echothiophate iodide for ophthalmic solution)

## Tillyer Topics



E. WILLIAM TILLYER

# Modulation Transfer Function

There is a great deal of discussion today about the Modulation Transfer Function, or "M.T.F." M.T.F. refers to what you get out of a lens based on what you put in. Or, how good is the image in relation to the reality? It is used widely today in optics of all types.

All of us are aware of the marginal errors that are present when a lens is not properly designed. As a matter of fact, errors are always present to some degree—even in the best of lens designs. These are usually marginal astigmatic and oblique spherical errors, or vision reductions caused by lateral color blur.

Modulation Transfer Function takes all of these factors into account. Plus any surface defects that might affect resolution. And, in the form of a ratio, M.T.F. says that the lens' ability to create a sharp image is reduced by a factor. The factor is the ratio of the contrast or modulation that enters the eye to that which enters the lens.

Our problem with ophthalmic lenses differs from the problems involved with telescope or total light gathering lenses. Because we never use the whole lens at any given time.

Therefore, we must consider an ophthalmic lens as a series of connected 7mm or 8mm lenses and determine the M.T.F. in each area by analyzing the power, absorption and color errors. Then we can consider what base curves should be used to arrive at the best over-all performance. This will be based on the results from each section of the lens that will be used by the patient.

But design alone is not enough. An M.T.F. measurement would show that without top quality surfaces the resolution is not what it can be.

Therefore, the importance of a fine ophthalmic surface must never be overlooked. If the surface is not the finest—even though the proper curves are used—the patient will not get the image reproduction implied in his Rx.

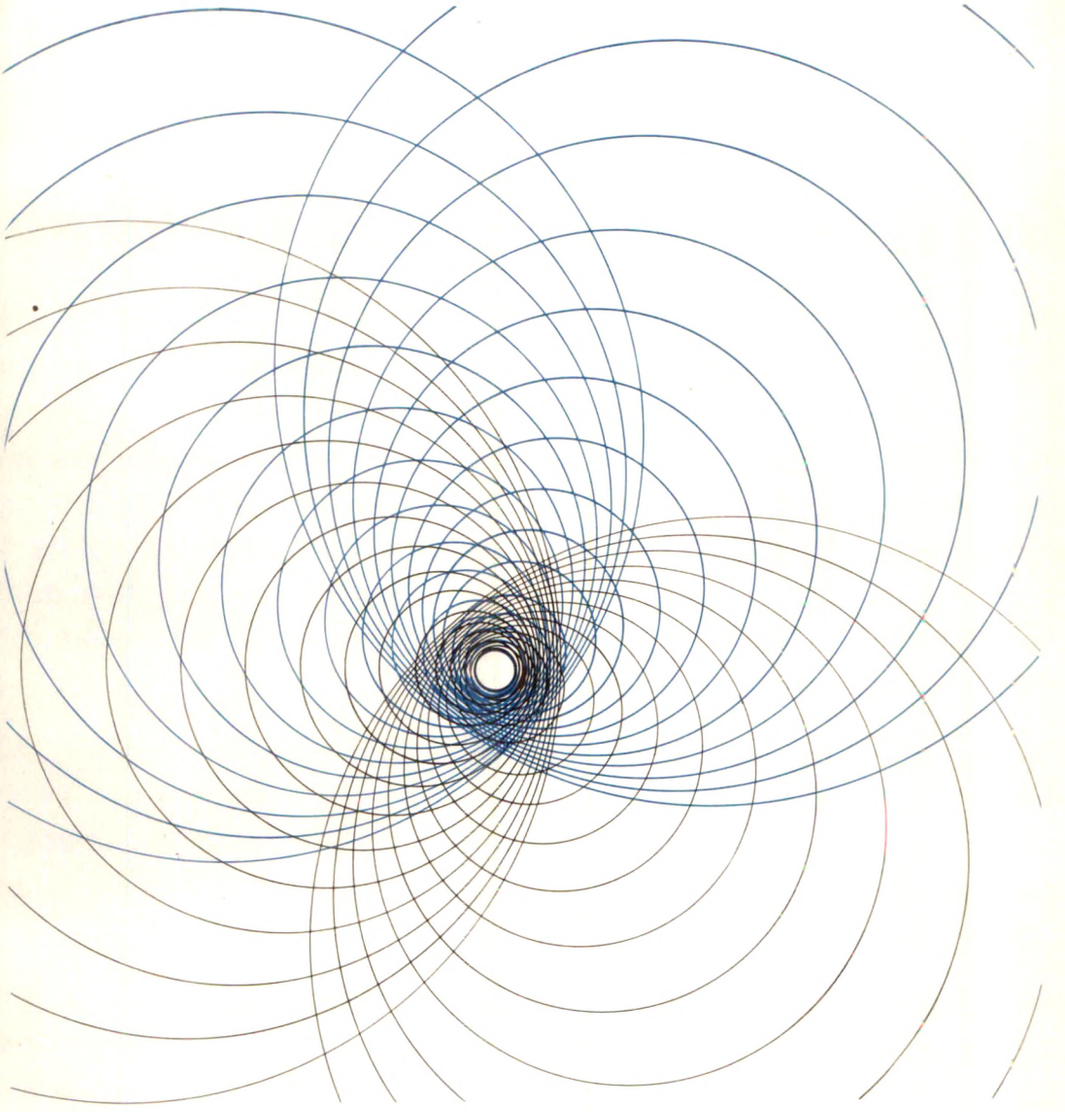
The deficiencies of the surface aren't usually picked up through the use of the Lensometer. Simply because scanning the entire lens, point for point, for waves, irregular surfaces or poor polish is a long and tedious job.

How, then, can you know which ophthalmic lenses will give your patients the best vision?

The answer is that you must depend upon the reputation of the manufacturer and the Rx laboratory. To duplicate the testing equipment required to determine which is the better lens would be extremely costly. Also to examine every lens would take too much of your valuable time.

So, in the final analysis, only by selecting lenses manufactured to the highest standards can you realize the accuracy of your refraction. And provide the patient with the fine vision to which he is entitled.

AMERICAN OPTICAL
CORPORATION
Optical Products Division • Southbridge, Mass. 01550



Project 117 unveiled...

...the new "Stellar" contact lens.

Aspherically engineered and designed for
a natural, more comfortable fit.

Danker & Wohlk, Inc.
635 Nassau Road, Uniondale, New York 11553

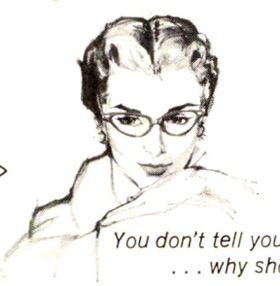
# When a trifocal is indicated... don't prescribe Younger Seamless Lenses!

**It has never been suggested that Younger Lenses were an "all-purpose" replacement for any well-designed, quality multifocal. Youngers are ophthalmically precise, *cosmetic* lenses, offering both distance and near fields invisibly. To the onlooker, they're exactly like single-vision lenses. Youngers are designed solely to bridge the *psychological* change in vision patterns and they don't make the patient look any older, as do the usual age-revealing, visible bifocals.**

**However, if the patient *needs* the three fields of a trifocal for efficient vision, even Younger lenses won't help. So we say . . . by all means prescribe the *finest quality trifocal* you can order. There is no substitute for trifocals when indicated, and your patient is entitled to the best you can provide.**

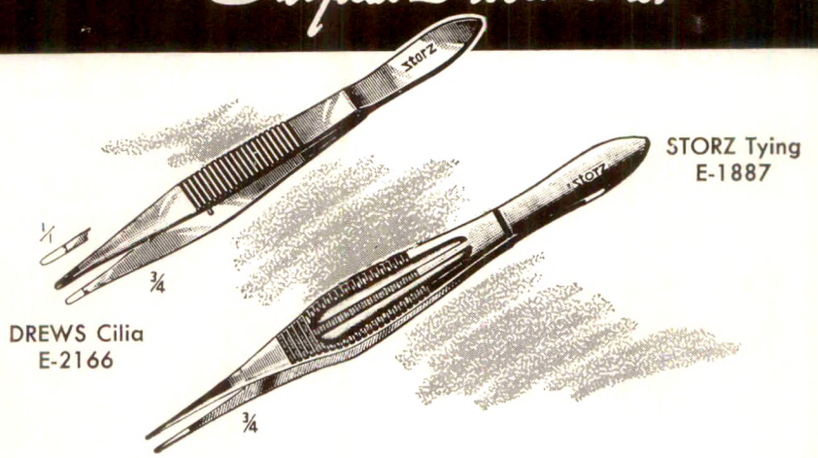
**NO FITTING PROBLEMS, NO LAB PROBLEMS with Youngers. If your patient has just graduated into the bifocal-wearing class (.75D to 1.75D adds seldom need an intermediate), help her or him (he's vain, too!) with the finest lens of its kind . . . Younger Seamless Lenses. Now available in Younger-Lite Hard Resin as well as glass, from most independent labs and all American Optical branches.**

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*You don't tell your age . . . why show it?*

storz
Surgical Instruments




STORZ Tying
E-1887

DREWS Cilia
E-2166

# Two Popular Ophthalmic Forceps

Drews Cilia and Storz Tying forceps are made with precision grasping surfaces. They are known to be dependable.

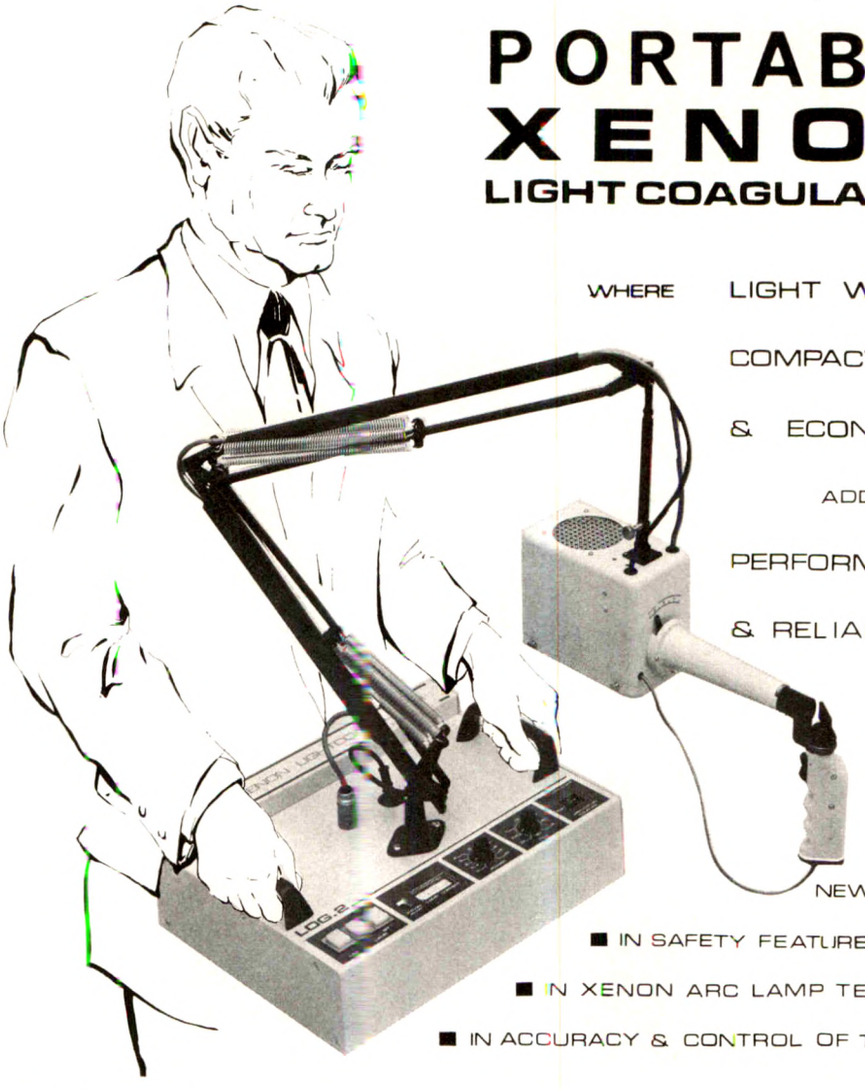
Both are further improved by increasing the strength of the shafts anterior to the delicate jaws. This added strength eliminates the spring and flexibility so the finely machined holding surfaces maintain their alignment regardless of force applied to the handles.

*Stainless Steel*

E-1887 • $25.50
E-2166 • $22.00

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FOR THE OFFICE, OUTPATIENT DEPT. OR SURGERY SUITE.



# PORTABLE XENON LIGHT COAGULATOR

WHERE LIGHT WEIGHT
COMPACTNESS
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NEW APPROACH

- IN SAFETY FEATURES.
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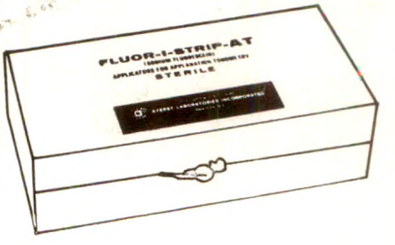


**When fitting contact lenses: to guard against the risk of infection inherent in the use of sodium fluorescein solutions, stain eyes with sterile Fluor-I-Strip-A.T. No excess fluorescein to stain the patient's face or clothing...water-proof grip to prevent staining of your fingers. Simply retract upper lid, apply dry orange tip of flexible applicator to the bulbar conjunctiva at the temporal side. For all these benefits: Specify Ayerst**





**FLUOR-I-STRIP®-A.T.**
**(sodium fluorescein)**
**STERILE OPHTHALMIC APPLICATORS.**




*Each applicator contains* not less than 1.0 mg. sodium fluorescein —provided by precise impregnation with a solution of sodium fluorescein and 0.5% chlorobutanol (chloral derivative), polysorbate 80, boric acid, potassium chloride, and sodium carbonate. *Supplied:* No. 1048—Boxes of 100 envelopes, each envelope containing 2 firm sterile applicators—one for each eye.

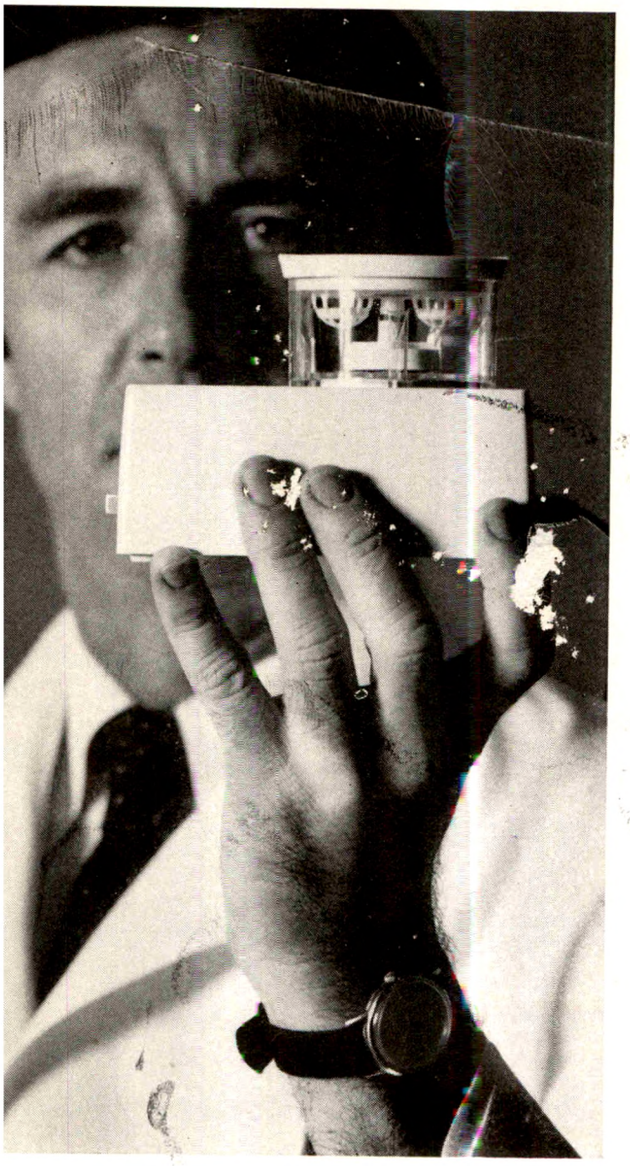
OPHTHALMOS DIVISION

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

7047

# Introducing
# SWIRL CLEAN™
## electric contact lens cleaner by Contique™

## the professional way to clean contact lenses



Until now, the most common method cleaning contact lenses has been to rub th between the fingers. As you know, this syst has three serious drawbacks: 1) it doesn't cle properly; 2) it *can* scratch or warp lenses; 3 may not be sanitary.

### A new, more efficient technique

The new Swirl Clean electric contact le cleaner by Contique approaches the problem a totally different manner: It combines t cleaning power of a high-speed agitator w the detergent action of Contique Cleaning So tion. The result is thorough but gentle clea ing—with a minimum of handling and le chance of lens loss.

Swirl Clean doesn't stop there. It provid a convenient place to soak and store lenses b tween wearings.

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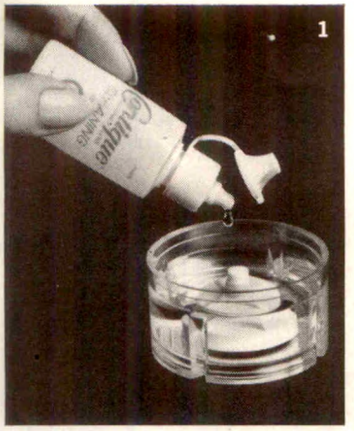
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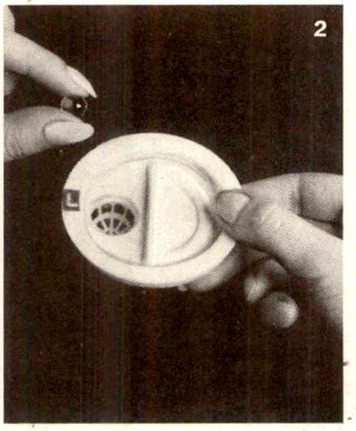
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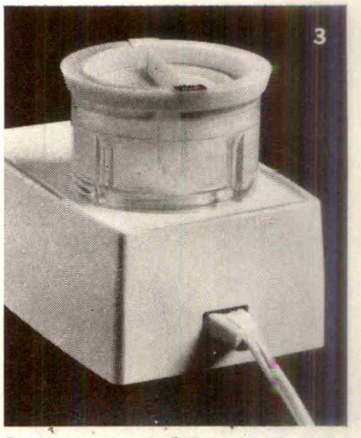
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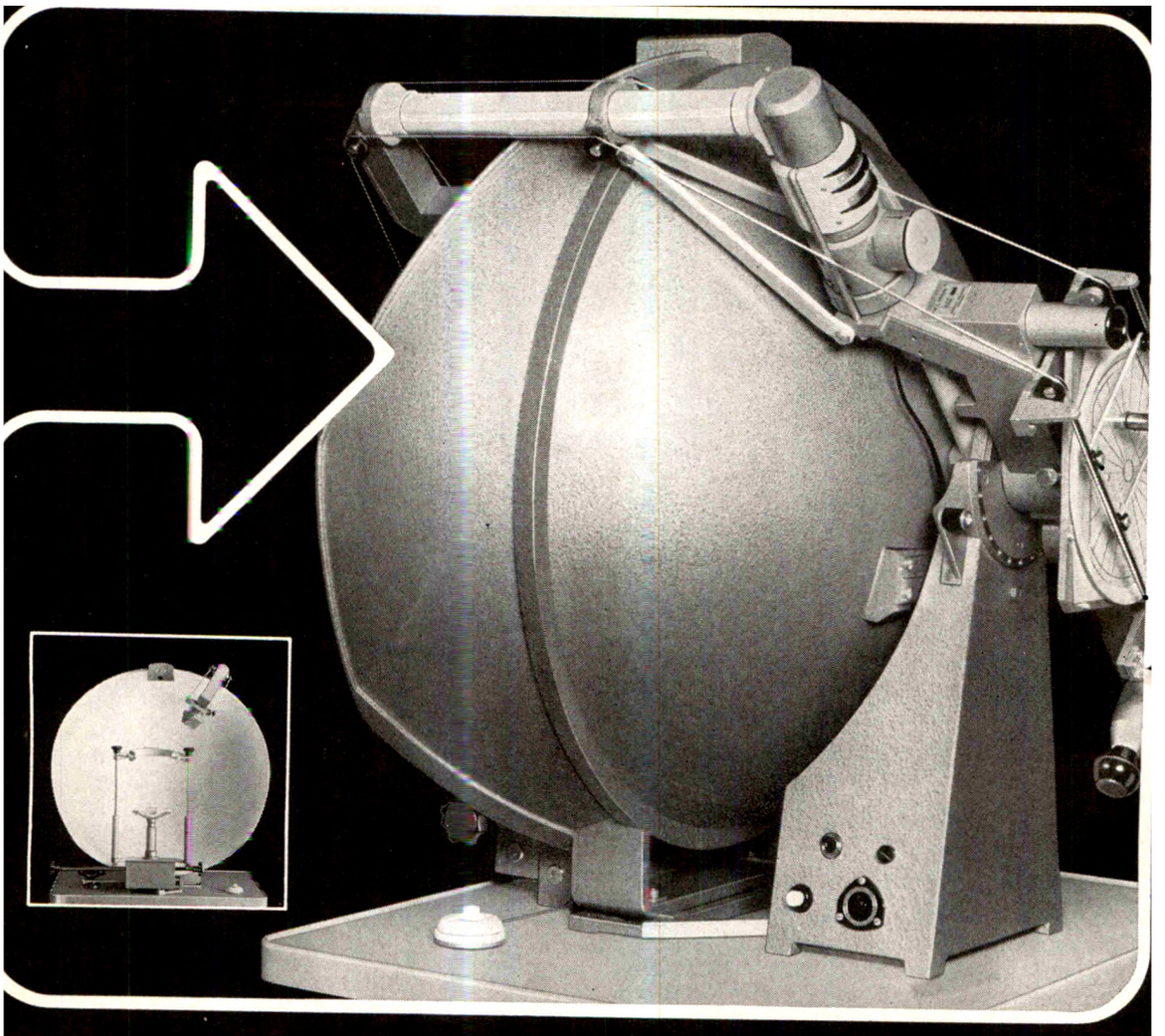



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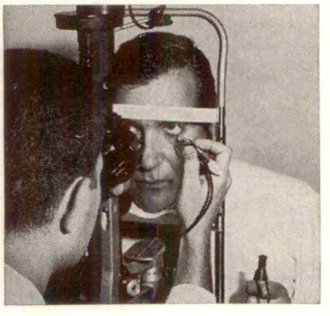
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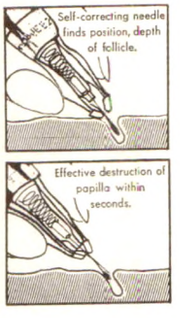
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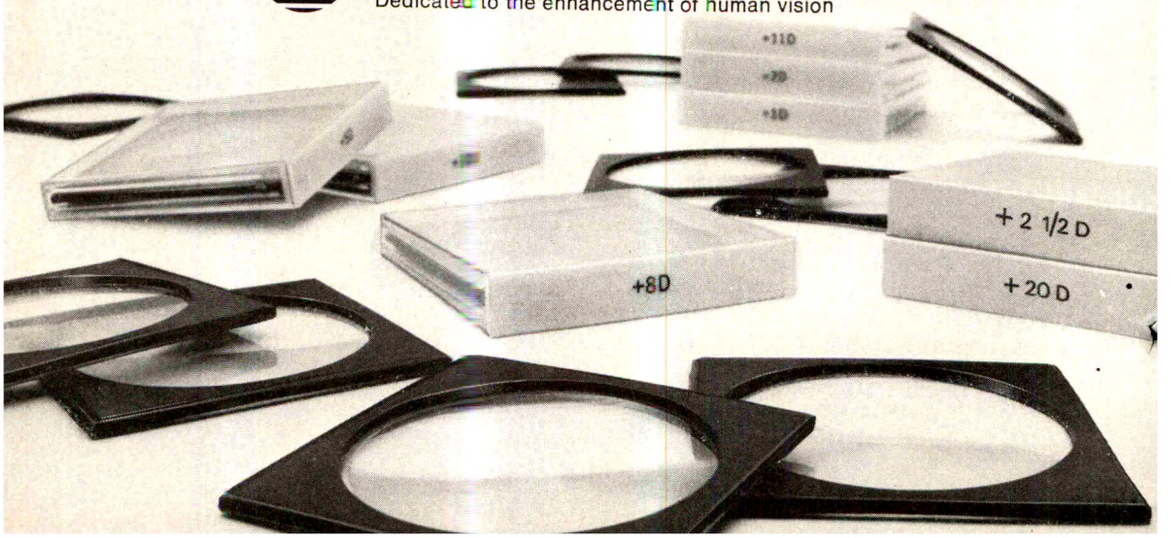
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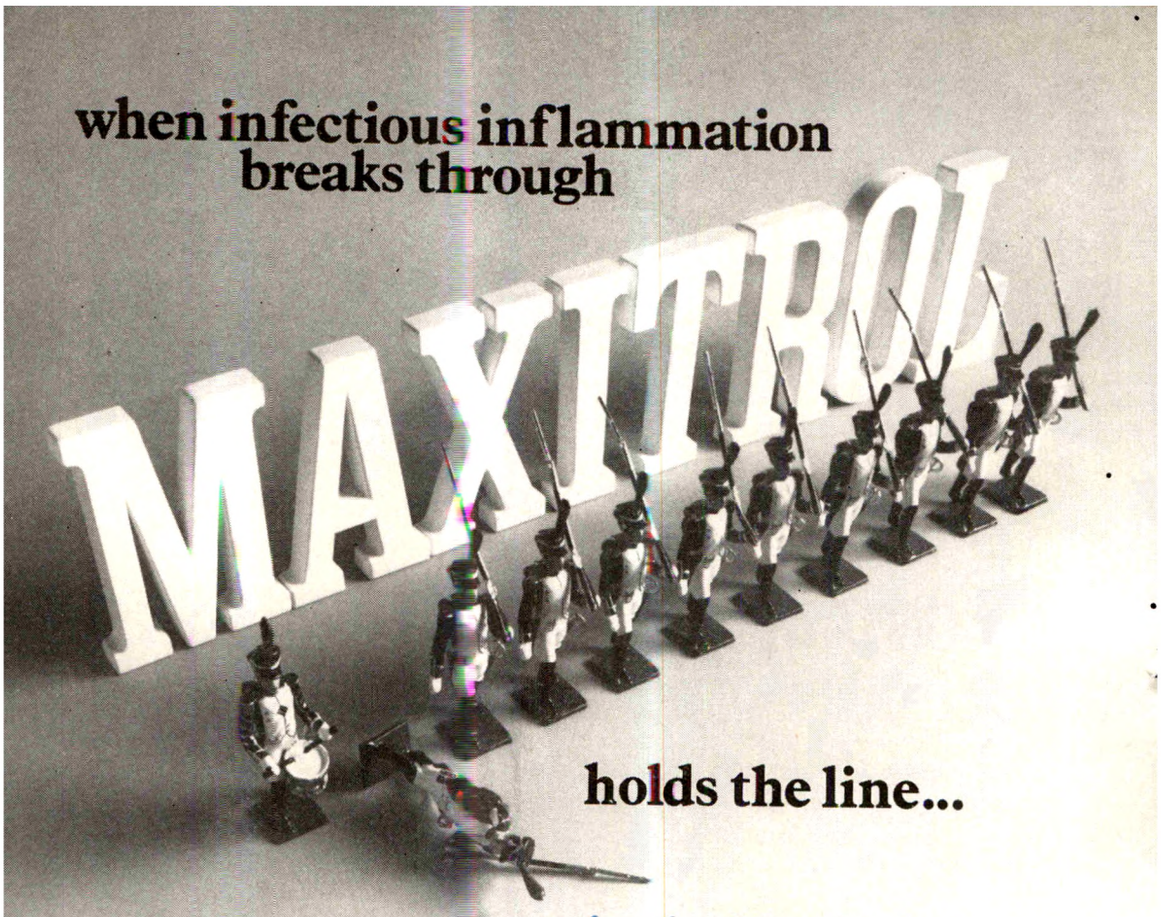
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References: 1. Nelson, E. L.: "Ophthalmic Steroids," in Kaufman, H. E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970. 2. Waltman, S. F. and Patrowicz, T. C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

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# MANAGEMENT OF CORNEAL PROBLEMS WITH HYDROPHILIC CONTACT LENSES

## A REPORT OF 30 CASES

JOHN W. ESPY, M.D.

*New York, New York*

Several earlier reports[1-6] describe the use of hydrophilic contact lenses for various therapeutic and optical indications. This paper reports the results in 30 consecutive patients with corneal diseases fitted with Griffin hydrophilic lenses at the Presbyterian Hospital during the past year.

### MATERIALS AND METHODS

*The lens*—The material used in the manufacture of the Griffin lenses is a combination of 2-hydroxyethyl methacrylate (HEMA), a hydrophilic polymer, mixed with other plastics. The chemical structure and characteristics of the HEMA polymer were described initially by Wichterle and Lim[7] in Czechoslovakia, and more recently by Gasset and Kaufman.[2] Because of the differences in the material and purification methods, the Griffin lens varies considerably from the other hydrophilic lens manufactured in this country (Soflens, Bausch and Lomb, Inc.). At the time of this study, the Griffin lens had not yet received FDA approval, and therefore, it was only available to investigators.

The main virtues of the Griffin lens are its index of refraction, softness, and ability to equilibrate with human tears. When fully hydrated, it is approximately 55% water by weight. In the hydrated state, the lens cannot fracture, but when it is dehydrated, it is quite brittle.

There is recent evidence that, unlike the original Czechoslovakian lenses, fluid and nutrients are exchanged through the Griffin lens in significant amounts. Whether this is adequate or not to maintain normal corneal metabolism is uncertain, but if this proves to be correct, tear flow and tear interchange would cease to be important considerations.

The Griffin lens is cut in the hard form, ground, and polished. The lenses are available in the following base curves: 7.2, 7.5, 7.8, 8.1, and 8.4 mm. The diameters of the lenses are 12.5, 13.0, 13.5, 14.0, 14.5, and 15.0 mm. Both surfaces are spherical. The inside surface of the edge has a bevel varying from 0.3 to 0.5 mm. The edge is thin but well rounded. The front edge has a lenticular cut to reduce thickness.

In fitting the lens, the curve–diameter relationship is the critical factor. A keratometer reading is useful as a starting point to get the base curve, and the lens should approximate the base curve of the flattest corneal meridian. The lens touches the central cornea and sclera arching the limbus. The diameter of the lens should be 2.0 mm larger than the cornea, thereby covering 1.0 mm of sclera around the limbus. The lens should center on the cornea with no restriction of eye movements, no movement with blinking, and no lens lag with rapid shift of gaze.

The Griffin lens is sterilized by soaking it in 3% hydrogen peroxide for five minutes,

From the Institute of Ophthalmology, Columbia-Presbyterian Medical Center, New York, New York.

Reprint requests to John W. Espy, M.D., 945 Lexington Avenue, New York, New York 10021.

followed by shaking the lens in normal saline buffered with 0.65% sodium bicarbonate for one minute. The lens is then shaken in normal saline for one minute, and placed in fresh saline for 45 minutes. Boiling the Griffin lens will cause deterioration. Eye medications cannot be used when the lenses are being worn, as the lenses will absorb the medication and concentrate the preservative, thus damaging the corneal epithelium.[2]

*The patients*—Without preselection, 30 consecutive patients with corneal diseases were fitted with Griffin hydrophilic contact lenses by following the curve–diameter relationship described above. All were outpatients. Initially, each was seen daily, the lenses were removed, and the cornea examined for any evidence of irritation by the lens. The lens was then sterilized and re-inserted. The time between examinations was gradually lengthened, depending on each patient's condition. Some patients were able to wear the lenses 24 hours a day from the start, and some removed the lenses at night. Several elderly patients with irritated eyes found it impossible to insert and remove the lenses themselves. No topical medications were used. To keep the lenses well hydrated, the patients were instructed to use a drop of saline every hour, but with adaptation the drops were used less frequently. The result was considered good if the condition was controlled or improved with the lens.

## Results

*Bullous keratopathy*—The largest group of patients treated were those with bullous keratopathy (Table 1). Their eyes became white and quiet. Although fitted primarily to relieve the symptoms of pain and irritation, there was an unpredictable improvement in vision. In some cases this was dramatic (in one case, 20/200 to 20/50). The improvement in the visual acuity appears to be due to a flattening of the large epithelial bullae, and not due to any significant change in stromal thickness or decrease of folds in Descemet's membrane. The use of 5% sodium chloride[2] appeared to have no effect, although it was well tolerated by all patients.

As in the eight cases reported by Lerman and Sapp,[4] all except one patient tolerated the lenses well. After a few weeks, these patients were seen only every two to three months for examination and sterilization of the lenses. One patient removed her lenses at night, but all others wore their lenses 24 hours a day. Some of the 11 successful patients have now been wearing their lenses constantly for over six months. The cause of the single failure is not clear, but the eye became red and irritated and the lens was discontinued after one week. No complications occurred in the remainder of this group.

*Neurotrophic and neuroparalytic keratitis*—The three patients with neuroparalytic keratitis from seventh nerve paresis (Table 2) had tarsorrhaphies, but the corneas continued to stain. The eyelid adhesions were released and they were fitted with lenses. They had immediate subjective improvement and the corneal staining cleared. The vision with the lenses in place was satisfactory. These patients remove the lenses at night, and taped their eyelids shut.

The two patients with fifth nerve lesions and neurotrophic keratitis had complete clearing of the epithelial irregularities and improvement in vision. One of these patients had previously worn a scleral lens, but it proved unsuccessful because of irritation and mucous problems. He had no difficulty with the hydrophilic lens, which he removes at night. The other patient had marked epithelial irregularity after an automobile accident. He wears the lens 24 hours a day for protection from the scarred and roughened upper eyelid.

*Corneal ulcers*—This group of patients (Table 3) was the most challenging because of the acute nature of the problems. All the patients had been treated for varying lengths of time with topical corticosteroids or antibiotics, or both, plus pressure dressings, without improvement. In each case, the bacterial culture was negative. The corneal ulcers in

TABLE 1

BULLOUS KERATOPATHY
(12 Cases)

| Age in Years | Etiology | Visual Acuity | | Hours Daily Wear | Weeks of Wear | Result |
|---|---|---|---|---|---|---|
| | | Without Lens | With Lens | | | |
| 65 | Fuchs' dystrophy | 20/80 ± | 20/30 | 24 | 42 | Good |
| 70 | Cataract extraction | Less than 20/400 | 20/60 ± | 24 | 35 | Good |
| 53 | Cataract extraction | 20/70 ± | 20/30 | 16 | 34 | Good |
| 74 | Cataract extraction | Hand motion | Hand motion | 24 | 24 | Good |
| 63 | Essential iris atrophy | 20/40 − | 20/20 − | 24 | 18 | Good |
| 77 | Cataract extraction | 20/200 + | 20/50 ± | 24 | 16 | Good |
| 80 | Cataract extraction | Less than 20/400 | 20/400 | 24 | 14 | Good |
| 80 | Cataract extraction | Less than 20/400 | 20/400 | 24 | 14 | Good |
| 81 | Cataract extraction | Less than 20/400 | 20/70 | 24 | 14 | Good |
| 66 | Cataract extraction | Less than 20/400 | 20/200 | 24 | 10 | Good |
| 70 | Cataract extraction | 20/70 ± | 20/50 ± | 24 | 3 | Good |
| 59 | Cataract extraction | 20/80 ± | 20/80 ± | 24 | 1 | Poor |

TABLE 2

NEUROTROPHIC AND NEUROPARALYTIC KERATITIS
(5 Cases)

| Age in Years | Etiology | Visual Acuity | | Hours Daily Wear | Weeks of Wear | Result |
|---|---|---|---|---|---|---|
| | | Without Lens | With Lens | | | |
| 63 | Acoustic neuroma | 20/30 | 20/30 − | 16 | 25 | Good |
| 55 | Acoustic neuroma | 20/80 ± | 20/20 | 16 | 24 | Good |
| 3 | Hemifacial atrophy | 20/80 ± | 20/30 | 16 | 10 | Good |
| 21 | Auto accident | Less than 20/400 | 20/20 | 24 | 42 | Good |
| 67 | Fifth nerve resection | 20/200* | 20/80 + | 16 | 27 | Good |

* With scleral lens.

TABLE 3

CORNEAL ULCERS
(6 Cases)

| Age in Years | Etiology | Visual Acuity | | Hours Daily Wear | Weeks of Wear | Result |
|---|---|---|---|---|---|---|
| | | Without Lens | With Lens | | | |
| 47 | Radiation | Less than 20/400 | Less than 20/400 | 24 | 11 | Poor |
| 55 | Degenerating transplant | Less than 20/400 | 20/40 | 24 | 10 | Good |
| 67 | Herpes zoster | 20/200 | 20/40 | 24 | 6 | Good |
| 60 | Thyroid ophthalmopathy | 20/20 | 20/20 | 24 | 5 | Good |
| 68 | Metaherpetic | Less than 20/400 | Less than 20/400 | 24 | 4 | Poor |
| 63 | Metaherpetic | Less than 20/400 | Less than 20/400 | 24 | 2 | Poor |

the two patients with disciform keratitis (metaherpetic), the indolent ulcer in the patient with thyroid ophthalmopathy, and the case of radiation keratitis all involved the deep stroma. The other two involved the anterior stroma.

The patients were fitted with the lenses and followed daily. The two cases of disciform keratitis did not improve. The eyes became red and more irritated. The lenses were discontinued, and the patients were hospitalized, where one responded to topical corticosteroids and microthermy with the ulcer filling in. The other patient did not respond to similar treatment and the cornea perforated several months later.

The only complication in this study occurred in a patient who received extensive radiation to the right antrum for carcinoma of the antrum. The skin around the right eyelids was severely affected, and the cornea broke down. She was extremely uncomfortable, and had marked subjective improvement for several weeks after being fitted with a lens. However, over a weekend, she developed a severe superficial infection under the lens, and a 4 mm sterile hypopyon developed. She was admitted to the hospital and initially she responded to conservative treatment. Two months later the cornea dissolved and perforated. This was followed by an expulsive choroidal hemorrhage, and the eye was enucleated.

The patient with thyroid ophthalmopathy had a deep indolent ulcer near the limbus at approximately five o'clock. After wearing the lens continuously for five weeks, there was minimal vascularization from the limbus and the ulcer filled in with fibrous tissue. In the two patients with superficial ulcers, in one case due to a degenerating graft and the other to herpes zoster, the epithelium regenerated while wearing the lenses. These patients wore the lenses 24 hours per day. The staining completely cleared and the vision improved dramatically. When their eyes had healed, the lenses were removed, and there have been no recurrences.

*Keratitis*—Five patients were treated for keratitis (Table 4). One patient with keratitis sicca did not do well, because the vision was poor due to a high corneal astigmatism. The other patient with keratitis sicca, and the three patients with superficial punctate keratitis following cataract extraction, tolerated the lenses well; vision was good, and

TABLE 4

KERATITIS
(5 Cases)

| Age in Years | Etiology | Visual Acuity | | Hours Daily Wear | Weeks of Wear | Result |
|---|---|---|---|---|---|---|
| | | With Lens | Without Lens | | | |
| 35 | Sicca | 20/50± | 20/20± | 16 | 29 | Good |
| 28 | Sicca | 20/20 | 20/60± (High astigmation) | 2–4 | 8 | Poor |
| 60 | Aphakia with SPK* | 20/200–20/50 | 20/20± | 16 | 29 | Good |
| 51 | Aphakia with SPK* | 20/80± | 20/20± | 16 | 26 | Good |
| 80 | Aphakia with SPK* | 20/200 | 20/80± | 16 | 2 | Good |

* Superficial punctate keratitis.

the corneas did not stain. One has macular changes resulting in poor vision.

*Essential conjunctival shrinkage*—These two patients (Table 5) had dry eyes, scarred eyelids, and trichiasis due to pemphigus and Stevens-Johnson disease. Because damage occurs at night as well as during the day, the patients wear the lenses 24 hours a day. One of these patients did poorly because it was impossible to follow him adequately.

## DISCUSSION

Of the 30 patients fitted with the Griffin hydrophilic contact lens, 24, or 80%, responded favorably, indicating that these lenses are a useful adjunct in the management of some difficult corneal diseases. They act as a protective shield and prevent drying much as a tarsorrhaphy or conjunctival flap in neurotrophic keratitis, neuroparalytic keratitis, and corneal ulcers; but the results are often more satisfactory and the vision can be maintained. Furthermore, in cases where cautery of Bowman's membrane is indicated, as in bullous keratopathy, a hydrophilic lens gives adequate relief of the irritating symptoms and often some improvement in vision, as well. In cases of keratitis sicca and superficial punctate keratitis, where hard contact lenses are contraindicated, the hydrophilic lenses supply a precorneal source of fluid and prevent evaporation. For protection against scarred eyelids and trichiasis, as in pemphigus and Stevens-Johnson disease, they can be worn 24 hours a day without complications.

The poorest results in this study were with corneal ulcers involving the deep cor-

TABLE 5

ESSENTIAL SHRINKAGE OF CONJUNCTIVA
(2 Cases)

| Age in Years | Etiology | Visual Acuity | | Hours Daily Wear | Weeks of Wear | Result |
|---|---|---|---|---|---|---|
| | | With Lens | Without Lens | | | |
| 71 | Pemphigus | 20/70± | 20/30 | 24 | 16+ | Good |
| 12 | Stevens-Johnson disease | 20/100 | 20/50± | 16 | 6 | Poor |

neal stroma. Liebowitz and Rosenthal[5] reported a higher percentage of success, but in their cases the ulcers were mostly superficial, the epithelium was removed before fitting the lenses, and chloromycetin drops were used. The only serious complication occurred in the patient with severe radiation keratitis. In all other indications, a high success rate is predictable.

The mechanism by which the lenses produce their therapeutic effect may not only be due to the protective bandage shielding the eye and the fact that they supply a constant precorneal source of fluid. In addition, Liebowitz and Rosenthal suggest that the hydrophilic contact lens also provides a structural framework upon which the regenerating epithelium may grow.

Because a few patients experience some irritation initially, a gradual buildup in wearing time is preferable, when this is compatible with the disease being treated. However, there is no gross epithelial edema, as seen initially with hard lenses, and the lenses do not cause corneal staining. There is minimal conjunctival injection and the eyes are white and quiet. Except for one patient successfully treated for corneal ulcer, there has been no vascularization noted in patients wearing the lenses continuously for as long as nine months.

A small percentage of patients do not tolerate the lenses, although the reason is not apparent. Occasionally, even in a patient in whom the lens is successful, the eye will become red and irritated for no evident reason. If the lens is removed for a few days, usually it can be re-inserted and again well tolerated. Extremely careful follow-up is essential. Although the patients in this study were followed as outpatients, initial hospitalization for acute problems should be considered.

This study substantiates the results of others that hydrophilic lenses offer a valuable alternative in the management of difficult corneal problems. Because of the semirigid nature of the Griffin lens, it may offer certain advantages in some indications over a more flexible hydrophilic lens.

## Summary

Thirty unselected patients with bullous keratopathy, neurotrophic and neuroparalytic keratitis, corneal ulcers, keratitis sicca and superficial punctate keratitis, and essential shrinkage of the conjunctiva from ocular pemphigus and Stevens-Johnson disease were fitted with Griffin hydrophilic contact lenses. For acute problems, the lens was worn until the corneal lesion healed, and in chronic conditions the lens is worn permanently to control the disease and alleviate symptoms. Eighty percent of the patients reported responded favorably.

The lens is available in base curves ranging from 7.2 to 8.4 mm, and in diameters 12.5 to 15.0 mm. The curve–diameter relationship is critical in fitting the lens. The lens should touch the central cornea and sclera arching the limbus and extend 1 mm beyond the limbus. It should center on the cornea with minimal movement and cause no restriction of eye movements.

Sterilization of the lens requires approximately 50 minutes, during which time the lens is successively placed in solutions of hydrogen peroxide, buffered saline, and normal saline.

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# BIONITE HYDROPHILIC CONTACT LENSES USED AS COSMETIC DEVICES

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In evaluating reports of experience with the various hydrophilic contact lenses, it is important to bear in mind that each is a specific entity, having its own distinct physical and chemical characteristics.

Despite the warnings of certain investigators (Gasset and Kaufman[1,2]), the increasing number of published reports has tended to obscure this fact. These differences necessitate the development of specific techniques for use with a particular hydrophilic material. Many of the methods which have been developed for use with standard methyl-methacrylate lenses must be discarded or modified before being applied to lenses of another material.

This paper reports the results obtained in fitting 89 cosmetic cases with the Bionite* hydrophilic contact lens, employing a standard technique.

## MATERIALS

In general, the Bionite lens is available in powers ranging from plus 20 to minus 20 diopters. Four standard diameters are currently being manufactured (13, 13.5, 14, and 14.5 mm). In addition, each lens is available in any one of several radii of curvature (8.7, 8.4, 8.1, 7.8, 7.5, and 7.2 mm). Isotonic saline solution is supplied by the manufacturer in plastic bags containing 400 ml; Bionite capsules containing sodium bicarbonate are also offered. A 3% hydrogen peroxide solution may be purchased by the patient without prescription in any pharmacy.

## SELECTION OF CASES

Preliminary investigation with the Bionite lenses revealed that moderate to high degrees of corneal astigmatism cannot be corrected consistently (Kaufman and Gasset,[2] and Gasset[3]). Therefore, patients were excluded if their astigmatic error was greater than 1.50 diopters. In addition, all patients included in this series were free of active ocular disease, each had expressed a desire to wear cosmetic contact lenses, and each was willing to participate in the investigational program.

Although eventually all powers of lens will be available, at present plus powers are in short supply, and therefore this series includes only one patient with hyperopia.

## CALIBRATION OF LENSES

The trial lens set employed for this series consisted of only 10 lenses; these varied in radii of curvature from 8.4 to 7.5 mm and in diameter from 14.5 to 13.0 mm. The average power of the trial lenses employed was minus 3.00 diopters.

Although the lenses are delivered in individual containers marked with the various parameters, each lens was re-checked for accuracy of power, diameter, and radius of curvature. The power of the lens is ascertained by blotting both surfaces to remove excess moisture and then reading the power on a lensometer. The effectiveness of the Bionite lens is related to its state of hydration, so that one should read the power of this lens within a few seconds after blotting.

The radius of curvature (base curve) is measured with the optical gauger. This device is made up of a series of plastic studs whose distal extremities have been ground to the standard radii. By placing a lens over the various studs one can quickly ascertain the base curve of the lens.

The diameter of the lens was confirmed by placing it on a magnifying reticle.

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### Fitting procedure

Gasset[3] has recommended employing the keratometer reading as the starting point for the fitting procedure. In our hands this proved both cumbersome and misleading. We soon developed our own method of fitting, however, and can suggest the following standard procedure: The ideal lens diameter is 1.2 mm greater than the corneal diameter, so we suggest starting with a lens 14.0 to 14.5 mm in diameter. In addition, experience has demonstrated that the long-term results are far superior with a lens that has a relatively flat radius of curvature. Therefore, initially we always select a lens with an 8.4 mm radius of curvature and a diameter of 14.0 or 14.5 mm. We make no attempt to correlate the power of this first lens to the patient's actual refraction. After insertion of the lens, patients invariably experience a mild foreign-body sensation which lasts approximately 30 seconds. As soon as the patient is comfortable the lens is inspected. First, we ascertain that the diameter is approximately correct and second, we check the stability of the lens on the cornea. The lens should move readily with each blink and there should be some small degree of displacement with lateral or downward gaze. At this stage, corrections may be indicated: The diameter may be altered if necessary, a steeper lens may be employed if the adherence is grossly inadequate, or a flatter curve may be necessary in cases where the motion is obviously inadequate. After the fitting is satisfactory, the trial lens is then worn for 20 minutes to allow for stabilization. When 20 minutes have elapsed, the lens is re-inspected to ascertain that the lens is not adhering excessively to the cornea; if not, the over-refraction may be performed. In performing the over-refraction, the retinoscopic image often provides an excellent clue as to the resultant visual acuity—the aim is to obtain a consistently clear 20/20 acuity which does not seem to vary with blinking. Theoretically, we anticipate that the spherical equivalent of the manifest refraction will be within one-half diopter of the power of the prescribed Bionite lens. The algebraic sum of the over-refraction and power of the trial lens equals the power of lens to be ordered.



Fig. 1 (Aquavella, Jackson, and Guy). Diagram showing the lens-cornea interface area in a proper fit relationship.

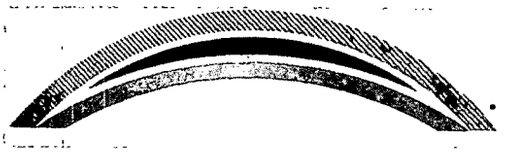


Fig. 2 (Aquavella, Jackson, and Guy). Diagram showing the lens-cornea interface area when the lens is too steep.

A cross section of the interface area in a case of proper fit (Fig. 1) reveals only a very thin tear film layer interposed between the lens and the cornea. If the lens is too steep, the interface area will have a plus lens effect (Fig. 2) and in the process of over-refraction the patient will accept an unusually high amount of minus correction. In addition, if the patient blinks, the interface area will tend to collapse, temporarily eliminating the plus tear film, and producing a variability both in the subjective acuity and in the objective retinoscopic reflex.

With the completion of the over-refraction, the specific lenses may be ordered with the correct diameter, radius of curvature, and power.

### Insertion and removal

We advocate that the patient receive preliminary instruction on insertion and removal at the first visit. In addition, we supply a sample lens so insertion and removal may be practiced at home. In this way, the patient quickly becomes adept and the initial experience is with an expendable lens rather than with the specially ordered material.

The recommended technique is as follows:

*Insertion*—The patient places the lens on

the index finger, looks up and holds the eyelid down with the other hand. He then places the lens on the inferior sclera, presses gently, and closes the eyelids.

*Removal*—The patient looks up and pulls the lower eyelid down, exposing the inferior bulbar conjunctiva. With the tip of the index finger the lens is moved down and pinched against the thumb. This permits air to pass under the lens, facilitating removal.

### Sterilization and storage

The recommended daily procedure was developed specifically for Bionite lenses by Gasset, Kaufman, and Morrison[4]; it is effective against bacteria, fungi, and herpes simplex virus. Furthermore, its routine use adds durability and strength to the new lenses. The procedure requires only a few minutes at bedtime.

On retiring, the lenses are placed in the case and the case is filled with hydrogen peroxide 3%. After five minutes the peroxide is discarded. The case is then filled with normal saline solution and the contents of a Bionite capsule, containing a pre-measured amount of sodium bicarbonate USP. After a one-minute soak in this solution, the solution is discarded and the lenses are rinsed four or five times with sterile normal saline. The case is then refilled with sterile saline and the lenses are allowed to soak overnight. Before insertion in the morning, the lenses are soaked again in a fresh change of sterile normal saline solution.

### Delivery

Prior to their delivery to the patient, the lenses are rechecked as to the accuracy of the power, diameter, and radius of curvature. Following this, they are sterilized. At the time of delivery, the lenses are inserted and after 20 minutes visual acuity and accuracy of fit is rechecked. Patients are instructed to wear their lenses during essentially all their waking hours. With properly fitted Bionite lenses no gradual increase in the wearing time is necessary.

### Results

Of 89 cases (178 eyes), there were 82 successes (92%); 78% achieved 20/20 vision, 11.2% had 20/25, and 3.4% had 20/30.

There were seven cases (8%) termed as failures. Final visual acuity in 7.4% of the 178 eyes was 20/40-20/60. Cases considered failures are as follows:

Case 1 is a young attorney who was unable to wear standard methylmethacrylate lenses. He reported variable acuity with the Bionite lenses, and complained of difficulty with insertion and removal.

Case 2 was termed a failure because the patient could not achieve good acuity, although she demonstrated no significant residual astigmatism.

Case 3 did well and reported good stable acuity without adverse effects, but this patient was advised by her allergist not to wear contact lenses.

Cases 4 and 5 were patients who were very apprehensive and nervous individuals who could not master the insertion and removal technique. They both have narrow interpalpebral fissures. Case 4 developed blepharospasm and a tendency to over accommodate when wearing the lenses.

Case 6 was unable to achieve satisfactory acuity due primarily to residual astigmatism.

Case 7 demonstrated good acuity but could not master insertion and removal.

Three of the successful cases deserve further comment. One has high myopia (−9.50) with two and one-half diopters of astigmatism in one eye. She has a significant amount of residual astigmatism in this eye and her acuity with the lens is only 20/60. The fellow eye has less astigmatic error and adequate acuity. The patient is happy and comfortable.

Another is a 14-year-old student with a personality problem who absolutely refuses to wear spectacles, despite a significant refractive error.

A third patient is a 16-year-old high school athlete who has difficulty participating in sports while wearing spectacles. Despite a

significant degree of residual astigmatism resulting in 20/40 vision, he is comfortable and enjoys his lenses for this purpose.

## Discussion

Fluorescein and other dyes must not be used with hydrophilic lenses as the dye will become incorporated within the lens. The lenses should be removed before instilling eye medications. If a disease develops which requires the wearing of a "bandage" hydrophilic lens and the instillation of medication, a special lens should be provided for wear during the treatment period in order to prevent the incorporation of the medication into the cosmetic lens.*

If the patient is having difficulty in wearing the lenses comfortably, or if he reports corneal injection or slight irritability with varying visual acuity, it is important to recheck the lenses for changes in diameter or radius of curvature. Most of these difficulties are caused by lenses that are "too tight." If that is the case, the patient will invariably be more comfortable with a lens of increased radius of curvature. Some of the earlier Bionite lenses had a tendency to become steeper when the fitting was "too tight." With improved manufacturing technique, this is no longer a common occurrence.

Isolated epithelial edema was rarely observed and always responded to selection of a flatter or thinner lens; restriction of wearing time did not become necessary. One recurring problem was the splitting of the lenses by the patient. Women patients with long fingernails, who had not completely mastered the removal technique, often scratched or nicked their lenses during the process of removal, and a lens so damaged tended to split either then or later. In addition, if the there were small nicks or defects in the lens periphery that had escaped the scrutiny of the manufacturer's quality control inspection, such lenses would be predisposed towards splitting when, on wearing, they were flexed in the appropriate axis.

Splitting has been satisfactorily controlled by a combination of several measures. Because of improved quality control by the manufacturer, all lenses are now free from peripheral defects on delivery. Patients are now given full instructions on insertion and removal, and this, combined with the policy of lending the patient an expendable lens on which to practice these techniques, has lessened the risk of such damage. In addition, our technicians now routinely instruct all women patients to trim the fingernails of the thumb and index finger of both hands prior to manipulation of their lenses.

If the patient notices a foreign-body sensation after insertion of the lens, he is instructed to remove the lens and clean it between the thumb and forefinger with saline to remove lint or other small dust-like particles.

On occasion some of the patients have reported falling asleep with the Bionite lenses in place. These episodes have not resulted any problems. Bandage lens wearers (not included in the present series) are often able to wear their lenses 24 hours a day for several months without discomfort or adverse effects. It is possible for cosmetic lens wearers to report on their progress by telephone, although office visits are advisable after the first and second week.

Because of the degree of adherence between the cornea and the lens, it is extremely difficult for a Bionite lens to loosen enough to fall out. Several patients said they were able to wear their lenses while swimming.

The Bionite lenses may be worn comfortably all waking hours from the first day of wear. No gradual increase in wearing time is necessary to achieve maximum comfort. All of our cases have demonstrated a lack of spectacle blur, and patients have been able to change from their spectacles to their contact lenses and back to their spectacles without

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* When the Bionite hydrophilic material is used as a bandage in the treatment of corneal disease,[1,3] the technique employed in fitting such a bandage lens differs considerably from that advocated in the present communication.

the usual difficulties encountered by methylmethacrylate lens wearers.

The fact that the Bionite lenses can be worn comfortably for long periods of time is undoubtably due to their inherent fluid and oxygen permeability. This factor probably accounts also for the low incidence of epithelial edema. Gruber[5] reports a comparative lack of permeability to oxygen in his experience with another hydrophilic material (Soflens). He also found that it was necessary to increase the wearing time slowly, despite the fact that the lens used in his study possessed a flexibility similar to the Bionite lens. This suggests that oxygen and fluid permeability may be critical factors in this respect as well.

Although a comparatively elaborate trial set is supplied, the great majority of patients can be fitted quickly and easily with one or two lenses. Certain factors may alter this situation, however. The patient with a narrow palpebral fissure, or one who has difficulty in learning insertion technique, might best be fitted with a lens of a relatively smaller diameter. An individual who is interested in wearing his lenses primarily for sports such as football or swimming might be better served with a larger diameter lens to lessen the possibility of loss. Although the overwhelming majority of patients are quite happy with the acuity that they obtain with the Bionite lenses, many individuals do demonstrate a small degree of residual astigmatic error. The manufacturers plan to produce a toric lens in the near future. This should prove very helpful in correcting moderate to high degrees of astigmatism.

Currently, a much more simplified system for storage and sterilization is under investigation which will eliminate the necessity of the hydrogen peroxide, bicarbonate, and saline solutions.

In its present form the Bionite lens offers immediate comfort combined with increased safety and a simplified fitting procedure.

## Summary

Bionite hydrophilic contact lenses were fitted in 89 cosmetic cases, according to a standardized routine. There were 82 wearers who were successful, representing 92% of those fitted. The new lens material offers the advantages of safety, comfort, and comparatively simple fitting procedure in individuals with less than one and one-half diopters of astigmatism.

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# A THERAPEUTIC EVALUATION OF HYDROPHILIC CONTACT LENSES

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Early experience with the use of hydrophilic contact lenses in selected corneal disorders has been encouraging, particularly in patients with corneal ulcers, neuroparalytic keratitis, Stevens-Johnson syndrome, and ocular pemphigoid disease. This report describes the findings in 45 patients (54 eyes) with corneal diseases who were hospitalized at the New York Eye and Ear Infirmary and treated with hydrophilic lenses.

## MATERIALS AND METHODS

Since hydrophilic lenses had not yet been approved by the Food and Drug Administration when this study took place, all patients were advised of the experimental nature of the lens trial and all were admitted to the New York Eye and Ear Infirmary. Routine blood work, smear, culture, sensitivity, and photographic studies were made and each patient was examined twice daily with the Haag-Streit slit lamp.

Lenses were inserted on the morning of admission and patients were allowed to wear them for four to eight hours the first day, when they were then removed, sterilized, and reinserted the following morning for a full day's wear.

The lenses used in the study (Soflens) are manufactured by Bausch and Lomb Company. They are composed of a polymeric hydrophilic gel, 2-hydroxy-ethyl methacrylate (HEMA) which absorbs approximately 40% of its weight in water or normal saline. When hydrated, the lenses are soft, pliant, transparent, and elastic. When allowed to dehydrate, they become brittle and crenated, and can be broken easily. Although the lens is hydrophilic in nature, tear exchange is still necessary for corneal oxygenation and nutrient transfer.

*Fitting the lens*—The lenses are pliant enough when wet so that keratometry readings for central posterior curvature is not essential. Instead, the lens power is determined by using the spherical equivalent of the basic refraction plus the vertex distance compensation; the lenses can then be adjusted by refraction over a trial lens.

*Sterilization*—Conventional contact lens wetting and cleaning solutions cannot be used with the soft lenses, nor can standard topical eye medications, because of the absorptive nature of the lenses which allows retention of the preservatives of the solutions, thus creating the possibility of damage to corneal epithelium. Daily sterilization is accomplished by boiling the lens for 15 minutes in a normal saline (0.9% NaCl) solution.

The lens should be stored and sterilized in isotonic saline. If the lens is stored in hypotonic solution or plain water, it will stick tightly to the cornea causing discomfort until the lens loses its tackiness by absorbing enough tears to approach isotonicity. Hypertonic saline will also cause discomfort, stinging, hyperemia, and lacrimation.

## RESULTS

The lenses were used for treatment of basically four problems: (1) corneal edema, (2) dry eyes, (3) corneal ulcers, and (4) a miscellaneous category that included mainly keratoconus, interstitial keratitis with corneal scarring, and post-keratoplasty dryness. The results of treatment are as follows:

*Corneal edema*—Six patients (six eyes) with advanced bullous keratopathy were treated with uniformly poor results. Although all the patients could tolerate the lens comfortably, in no case was there evident re-

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duction of corneal edema. Visual acuity, compared to spectacle correction, was unchanged in five cases, slightly worse in one. The instillation of normal saline or hypertonic saline (5%) drops did not significantly affect vision. Wearing time was also modified in an attempt to improve visual acuity, but neither all-day wear, part-time daily wear, or continuous wear provided any significant improvement in vision—in fact, 24-hour wear produced a slight increase in corneal edema, with no change in comfort. Patients did not report any improvement or change in vision during the late afternoon or evening hours as might have been expected in non-lens wearers with similar corneal pathology.

CASE REPORT

The only eye of this 55-year-old white man was affected with aphakia, bullous keratopathy, and glaucoma for many years; phospholine iodide and acetazolamide (Diamox) were required for control. His best visual acuity was 20/200 with aphakic correction. The cornea showed superficial blotch staining with microcystic and stromal edema and prominent corneal guttata. The pupil was irregular because of posterior synechiae and lens capsule remnants. A trial with the hydrophilic lens provided no change in vision or edema, even when hypertonic (5%) NaCl solution was instilled every two hours.

In all advanced cases in this category no change was noted in vision or edema, even when hypertonic sodium chloride solution was instilled every two hours. In all cases of bullous keratopathy treated with a hydrophilic soflens, the only tangible improvement noted was a variable increase in comfort in the majority of patients.

*Dry eyes*—Thirteen patients (18 eyes) were treated in this category, which includes keratitis sicca, Stevens-Johnson syndrome, ocular pemphigoid with symblepharon, and exposure keratitis. Patients in this category generally responded favorably to hydrophilic lens wear. Nine of the 13 patients were able to tolerate the lens with no discomfort, even on the first insertion. Wearing time varied; some wore the lens only during waking hours, and others wore the lens around the clock, but in all cases, sterilization was performed daily. Stipple staining and blotch staining, reflecting corneal dryness, was seen both before and after lens wear.

CASE REPORT

This 26-year-old mechanical engineer had a history of Stevens-Johnson syndrome from the age of 11 years, resulting in cicatricial entropion, symblepharon, and trichiasis in both eyes. By the age of 21 years, the patient had undergone four mucous membrane graft operations and at least three procedures for stenosis of the right nasolacrimal apparatus. The patient was unable to tolerate flush-fitting scleral lenses, but maintained 20/20 vision in both eyes, with frequent instillation of lubricant drops. During the trial with hydrophilic lenses, the patient was able to tolerate all-day wear comfortably. The cornea showed no edema but punctate stain was still present. He was troubled initially by flare and glare and significant peripheral distortion, particularly for reading and near work. His best visual acuity was 20/20 in both eyes.

Eyelid tonus, mechanics, and scarring proved to be very important factors in determining the success or failure of hydrophilic lens wear, as the following case demonstrated.

CASE REPORT

In 1955, this 23-year-old man developed Stevens-Johnson syndrome with marked symblepharon, cicatricial entropion, trichiasis, and subsequent corneal pannus. Both eyes were treated with a tarsorrhaphy from 1957-1964, and the patient has worn scleral lenses continually since 1965. A trial with hydrophilic lenses was unsuccessful despite frequent normal saline application because of the lens edges and extrusion by the scarred, thickened eyelids. Despite the use of normal saline drops applied every five minutes, the lenses could not be retained.

This case demonstrates that in severe drying conditions, as the lens loses its flexibility, it is easily displaced by thickened and scarred eyelids, especially when eyelid retraction and cicatricial entropion co-exist. Two other retention factors are the shape of the cornea and the presence of symblepharon bands. In the most advanced cases of corneal ectasia, secondary to advanced drying conditions, the lens is often expelled. Of great significance, however, in a case of ocular pemphigoid, following the lysis of symblepharon bands, a hydrophilic lens was tolerated and retained with improvement of corneal appearance and no symblepharon formation.

*Corneal ulcers*—The most dramatic results were seen in this category. A total of 11 patients (11 eyes) were treated, three with neuroparalytic keratitis and central ulcer, two with deep metaherpetic ulcers with stromal scarring, and six with deep chronic indolent ulcers that had not responded to other forms of treatment. Smears and cultures taken in all cases failed to reveal significant pathogens. In all 11 cases the lenses were tolerated without any discomfort, understandable since corneal sensitivity was reduced. Importantly, the lenses provided rapid epithelial healing of ulcers and slow restitution of corneal thickness. No scraping of the lesion was performed prior to the wearing of the lens.

### Case reports

This 55-year-old white man had a history of herpes simplex keratitis of 12 years duration and was treated initially with iodine scrub. The patient had recurrences over the next 18 months with stromal scarring. A fourth recurrence in 1960 healed quickly with IDU therapy and the condition was quiescent until September, 1968, when a central geographic ulcer developed and smoldered for six months, despite various treatment regimens. Visual acuity was 3/200. A trial with the hydrophilic lens provided significant and immediate comfort. The lens was worn continuously for 72 hours, with marked improvement in the appearance of the ulcer and complete healing within three weeks. Full corneal thickness is present 12 months later.

A 35-year-old white woman with atopic dermatitis, eczema, and severe eyelid and conjunctival involvement, developed a sterile indolent corneal ulcer in her right eye and secondary keratoconus in her left eye while wearing conventional methacrylate lenses. She was hospitalized for one month, but despite intensive local and systemic treatment and two epithelial debridements and ether cauterizations, the ulcer failed to respond. A hydrophilic lens was applied and the ulcer healed within 48 hours.

The ability of corneal ulcers to fill in under soft contact lens was demonstrated both in phakic and aphakic eyes. In the two aphakic cases, the ulcer was associated with interstitial keratitis in one, and a very soft eye secondary to retinal detachment in the other. In both cases the healing was complete, but required four to six days, somewhat longer than in the phakic group. Only one corneal ulcer failed to heal in this group. This case was a 25-year-old man who developed an indolent ulcer at the margin of a penetrating keratoplasty done for a chemical burn. However, under the lens, the progression of the ulcer was halted, allowing time to secure good donor material for subsequent keratoplasty.

*Miscellaneous group*—Fifteen patients (18 eyes) were treated in this group, which comprised mainly keratoconus, interstitial keratitis, and post-keratoplasty problems. In keratoconus of moderate degree (below 52 D in both meridians in the visual axis), remarkably good visual results were obtained despite the degree of corneal astigmatism. Of course, in these cases better vision can be obtained with hard lenses. Disappointing visual results were seen in cases of advanced keratoconus. In two of the 15 cases affected with interstitial keratitis, the patient experienced improved vision that was not possible with other lenses. Post-keratoplasty fittings are indicated when dryness is a factor. The advantage of hydrophilic lenses over conventional methacrylate lenses is that they can be fitted within a month or sooner, postoperatively. Nonetheless, care should be exercised in observing for edema and increasing vascularization. Vascularization appears to be less stimulated by the soft than the hard lens.

### Discussion

There is little doubt that the present hydrophilic lenses function efficiently as a protective patch and reduce eyelid and external irritative factors to allow healing and epithelialization. Unlike glued-on lenses, hydrophilic lenses provide a flexible treatment modality that can be altered as necessary. In general, the lenses are well tolerated by both normal and some diseased corneas, although in some cases prolonged wear produced edema, indicating some effect on oxygenation and tear exchange, not unlike hard lenses.

In this series, the lenses proved most useful in the treatment of indolent, noninfectious corneal ulcers. Visible improvement of-

ten came within 24 hours, and all patients were comfortable. Visual acuity was improved secondarily as tissue healing progressed.

Dry eyes also responded well to hydrophilic lenses, with immediate improvement of comfort, even though the fluorescein staining pattern often showed no change. Visual acuity was as good or only slightly poorer than that obtained with spectacles or hard lenses. However, in severe cases with extensive scarring of the eyelids, the lenses were frequently pushed off the cornea by eyelid action. Normal eyelid tonus was essential to the maintenance of good lens centration and motility. In these cases, flush-fitting, hard scleral lenses still appear to be the most useful treatment aid, although hydrophilic lenses can be tried if symblepharon formation can be severed and normal eyelid position re-established.

There are several reports[1,2] of significant improvement of corneal edema and visual acuity in cases of bullous keratopathy, using other hydrophilic lenses. Our experience with the use of hydrophilic lenses in the treatment of advanced bullous keratopathy showed uniformly poor results in improving vision or reducing edema. Nonetheless, comfort and visual fields were improved to various degrees. It is important to differentiate between epithelial and stromal edema. The former responds well to both topical hygroscopic solutions and hydrophilic lenses, whereas in stromal edema comfort is improved but the edema is not affected.

## Summary

Therapeutic indications for hydrophilic lens treatment of corneal diseases were evaluated in 45 patients (54 eyes) whose disease could be categorized in four basic groups: corneal edema (six eyes), dry eyes (18 eyes), corneal ulcers (11 eyes), and a miscellaneous group (18 eyes). Six patients (six eyes) with advanced bullous keratopathy were treated. Poor results were seen when stromal edema was present. Neither visual acuity nor edema was improved; comfort and visual field were variably improved. The group with dry eyes consisted of 13 patients (18 eyes) with keratitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, and exposure keratitis. These were treated with significant improvement of comfort and maintenance of good vision. Hydrophilic lenses proved most useful in the treatment of 11 patients (11 eyes) with indolent, noninfectious corneal ulcers of varying depth. Fifteen patients (18 eyes) were treated with hydrophilic lenses which were well tolerated postoperatively in keratoplasty where dryness was a problem. In moderate keratoconus, and occasionally in interstitial keratitis, good visual results were obtained using hydrophilic lenses.

Hydrophilic lenses in this series provided the best results in the treatment of corneal ulcers and dry eyes and the poorest results in cases of advanced bullous keratopathy.

### Acknowledgment

We thank our chief resident, C. Frank Chambers, M.D., for significant help in following the patients reported herein.

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# BLEPHAROPTOSIS AS A COMPLICATION OF CONTACT LENS MIGRATION

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Contact lenses have been lost in the eyelid for periods of 12 days to 69 months.[1-6] One report[6] described mild blepharoptosis of the eyelid involved. Blepharoptosis in an adult who wears contact lenses should suggest the possibility that a lost lens may be embedded in the tissues of the upper fornix.

## CASE REPORT

A 29-year-old man was seen at Wills Eye Hospital on June 22, 1970. His chief complaint was that for the past three months, coincident with the period in which he resumed wearing contact lenses, he had experienced a white, mucous-like discharge from both eyes during the daytime, and his eyelids were stuck together each morning when he arose. Secretion was significantly worse in his right eye, and in the week prior to admission, his right upper eyelid had become slightly swollen. He had noted drooping of his right eyelid for 18 months.

The patient reported that he had worn glasses since childhood for moderate myopia. Contact lenses were fitted initially in August, 1967. Although his right eye was always a bit sore compared to the left, he wore his lenses 14 to 16 hours daily, removing them twice daily for cleaning and always removing them before retiring. He had lost his right lens two years earlier, and it was immediately replaced, but some months later, he discontinued wearing these lenses for an eight-month period. He resumed daily wear in May, 1970.

Past medical and ocular histories were not otherwise significant.

At the time of his first evaluation, visual acuity was RE:20/25, and LE:20/20 with his contact lenses in place. Vision in his right eye improved to 20/20 with the use of a pin-hole. External examination revealed about 2 mm of right blepharoptosis in the primary position. A bilobular clear cyst was present in the upper fornix medially. Applanation pressures were 15 mm Hg in each eye. The remainder of the ocular examination was normal. The patient was treated with 15% sulfacetamide drops four times daily.

On re-examination August 7, 1970, the blepharoptosis was worse and the cyst contained blood. He was admitted August 30, 1970. There was tumefaction of the right upper eyelid and 3 mm of right blepharoptosis (Fig. 1). The eyelid mass had two distinctly different, palpable areas. Centrally, at the upper margin of the tarsus, there was a firm, round mass approximately 1 cm in diameter. On eversion of the eyelid this mass was seen to be connected to a cystic lesion in the nasal third of the eyelid at the level of the superior border of the tarsus.

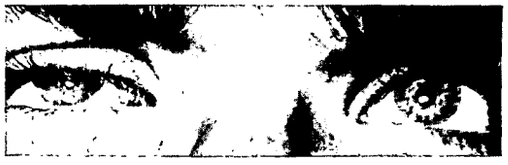


Fig. 1 (Yassin, White, and Shannon). Preoperative photograph showing blepharoptosis and thickening of right upper eyelid.

Systemic examination was within normal limits. Routine hemogram, urinalysis, and blood chemistries were unremarkable. Serology was non-reactive. Chest x-ray films and electrocardiograms were within normal limits.

On August 31, 1970, under general anesthesia, the right upper eyelid was everted with an Erhardt clamp. The superior aspect of the firm tarsus mass was incised and the edge of a contact lens immediately became visible. The incision was enlarged and the lens was delivered. The cystic area was simply incised and drained. A biopsy specimen of surrounding tissue was taken and later showed chronic inflammatory changes.

The patient made an uneventful recovery, and has returned to the use of spectacles with safety lenses on a permanent basis.

## COMMENT

This case indicates the need to examine carefully the superior cul-de-sac in any patient who demonstrates blepharoptosis and reports a history of contact lens loss. The need for such examination was stressed in similar case reports by Green[1] in 1963 and by Shenken[6] in 1969 of eyelid tumors containing a "lost" contact lens. Acquired blepharoptosis in patients who have lost a contact lens should arouse suspicion that the lens may be embedded in the soft tissues.

## SUMMARY

A lost corneal contact lens was found to have become embedded above the tarsal plate in a 29-year-old man who presented with ac-

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quired blepharoptosis of 18 months' duration and a mucous discharge over the most recent three months. Surgical removal of the contact lens was followed by prompt resolution of all signs and symptoms in this patient and restoration of an essentially normal eyelid. It is suggested that acquired blepharoptosis, particularly with tumefaction, in a contact lens wearer should indicate careful questioning as to the possibility of the earlier loss of a contact lens.

ACKNOWLEDGMENT

We thank Arthur H. Keeney, M. D., Ophthalmologist-in-Chief, Wills Eye Hospital and Research Institute, for his help in the preparation of this case report.

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OPHTHALMIC MINIATURE

. . . The circumstances of unfamiliar apparatus may raise the suspicion of the evil eye among unsophisticated peoples. The Irish painter Sir John Lavery (1856-1941) found it very difficult to persuade the natives of Morocco to pose, for the concentration of his eyes on them and the resulting picture, made it all too likely that the evil eye and magic were involved . . .

Gifford
The Evil Eye

# GRANULOMATOUS KERATITIS RESULTING FROM USE OF CYANOACRYLATE ADHESIVE FOR CLOSURE OF PERFORATED CORNEAL ULCER

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In recent years use of cyanoacrylate adhesive monomers has been advocated for a variety of ocular disorders. Because of the potential value of this technique in sealing certain types of corneal perforations, many laboratory investigations have been carried out to evaluate the efficacy of cyanoacrylate adhesives in this regard and their possible side effects upon the cornea. Although several clinical reports describe the successful use of cyanoacrylate monomers in sealing corneal perforations, we believe this is the first reported case in which a human cornea, treated with cyanoacrylate adhesive for a perforation, subsequently became available for pathologic study.

## CASE REPORT

In 1965, a 51-year-old white man underwent a penetrating keratoplasty of the right eye. Recurrent herpes simplex keratitis had caused extensive scarring of his right cornea. His left eye was blind following an accident in 1953. The graft in the right eye remained clear for six months, but the next 18 months were marked by episodes of graft edema with subsequent vascularization. This required treatment with topical and systemic corticosteroids. On July 26, 1968, the right cornea was treated by cryotherapy. Several days later the ulcer extended to the level of mid-stroma, and within four weeks a descemetocele was present at the corneal apex. On August 26, 1968, a 5.5 mm tectonic lamellar keratoplasty was done. The graft became cloudy and vascularized.

On October 9, 1968, the patient developed severe pain in the right eye and was found to have a corneal perforation with uveal prolapse. The host cornea and graft were opaque and vascularized. The corneal perforation was situated at two o'clock, about midway between the corneal apex and the limbus (Fig. 1). The uveal tissue prolapsed through

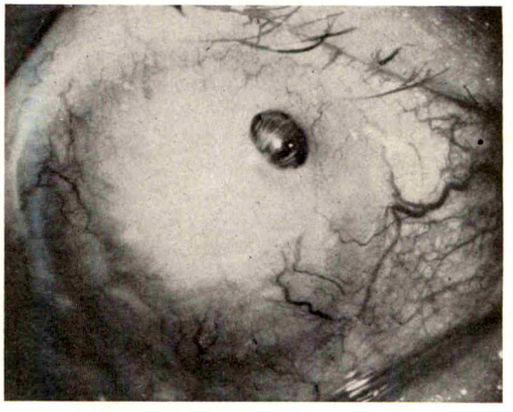


Fig. 1 (Ferry and Barnert). Right eye. Corneal perforation with prolapse of uveal tissue.

the defect was about 1 × 2 mm in diameter. Several hours later the prolapsed uvea was excised and the corneal perforation was repaired using isobutyl-2 cyanoacrylate monomer adhesive. This was done as follows: A cotton applicator was attached to one side of a polyethylene plastic disk, after which a small amount of the fluid cyanoacrylate adhesive was applied to the other surface. Using the applicator stick for manipulation of the polyethylene disk, the fluid cyanoacrylate adhesive was then apposed to the corneal perforation and held in place for 15 seconds. The applicator stick was then removed, after which the polyethylene disk was lifted away from the perforation site with forceps. It was seen that a satisfactory film of the adhesive material was in place, closing the corneal perforation. No leakage of aqueous humor was evident upon application of slight pressure to the eye. On the first postoperative day the adhesive patch was observed to be in place. There was no leakage from the wound. On the second postoperative day the adhesive patch was found in the superior fornix. The perforated area of cornea was closed over but a deep ulceration was still present. Because of diffuse corneal opacity, the patient's iris and anterior chamber could not be visualized satisfactorily.

On May 3, 1969, the patient was admitted for a second penetrating keratoplasty of the right eye. The host and donor cornea were extensively vascularized, chiefly peripherally (Fig. 2). The anterior chamber and iris were not satisfactorily visualized over much of their extent because of corneal scarring. Two days after admission, a 9 mm penetrating keratoplasty was performed and a mature cataract was concurrently extracted. Postoperatively, visual acuity in the right eye improved to 20/50, but subse-

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quently bouts of graft edema again developed despite intensive immunosuppressive therapy.

### Pathologic examination

Examination of the corneal button revealed a marked irregularity in thickness of the corneal stroma (Fig. 3). Over about one-half of the corneal button, the stroma was reduced to about one-third of its normal thickness and disorganized iris adhered to its posterior surface. In the remaining half of the corneal button, the stromal thickness appeared slightly increased, Descemet's membrane was interrupted but better preserved than in the other half, and only a small fragment of iris adhered to its posterior surface. Throughout the entire corneal button there was prominent stromal vascularization and a heavy infiltrate of inflammatory cells, chiefly plasma cells and lymphocytes. Particularly in the thicker half of the corneal button, many epithelioid and giant cells were scattered throughout the corneal stroma (Fig. 4). Examination of this area under higher magnification revealed the presence of innumerable "clear" areas occupied by the plastic material used to seal the corneal perforation. Foreign body giant cells enveloped many of these particles (Fig. 5). No other foreign material was present. Special stains for bacteria and fungi revealed no organisms. No inclusion bodies of the type seen in herpes simplex keratitis were observed in the epithelium, nor was there a granulomatous reaction to Descemet's membrane.

### Comment

The use of cyanoacrylate adhesives for surgical purposes was first reported in 1960.[1] The various cyanoacrylate adhesives produce tissue reaction, it generally being held that the shorter-chain homologues (methyl and ethyl) tend to produce more acute reactions,[2-7] while those with longer chains produce a foreign-body reaction, often with giant cells.[4-7] The inciting factor has been thought to be liberation of cyanide and formaldehyde as the material is degraded,[7] the actual heat liberated by the monomer as it polymerizes,[6] and the mechanical presence of the polymer.[3,8] In the eye, reactions have not been as severe as in some other tissues.[8-12] Among the reasons suggested for this[13] is that the amount of material used in ocular procedures is so small (large amounts cause considerable reaction).



Fig. 2 (Ferry and Barnert). Corneal vascularization and scarring immediately before the second penetrating keratoplasty (seven months after closure of corneal perforation with cyanoacrylate adhesive).

More rapid polymerization and lower tissue toxicity have been regarded as two advantages of the higher homologues over the lower homologues. But recently laboratory studies have been published in which the investigators were unable to demonstrate a difference in tolerance to various cyanoacrylates.[8,14]

Aronson and associates[14] have emphasized the biphasic character of the corneal inflammatory response to the various monomers.

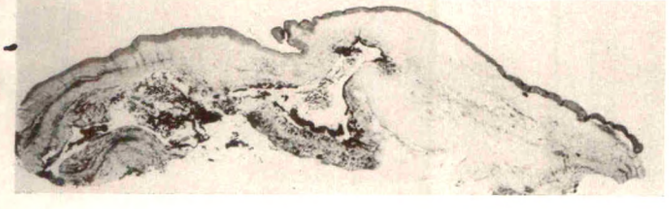


Fig. 3 (Ferry and Barnert). The corneal button removed at time of second penetrating keratoplasty. Stroma is of irregular thickness, vascularized, scarred, and heavily infiltrated by inflammatory cells. A large fragment of iris adheres to posterior corneal surface (hematoxylin and eosin, ×15).

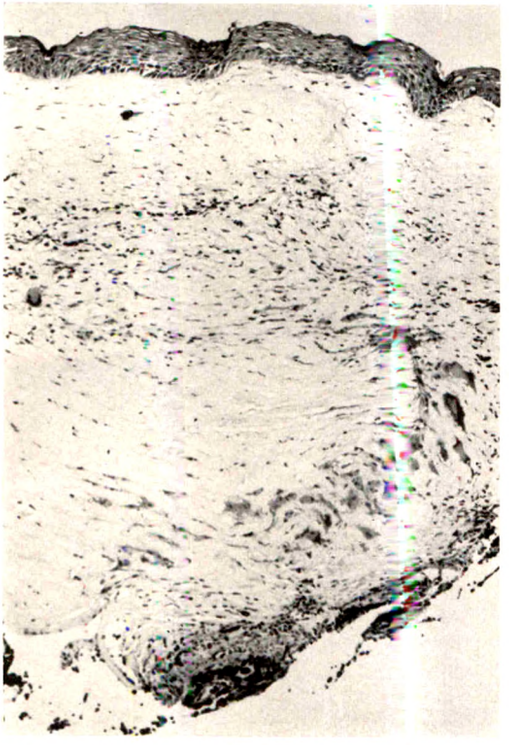


Fig. 4 (Ferry and Barnert). The right-hand side of corneal button shown in Figure 3. Stroma (mid- and deep) contains a prominent infiltrate of epithelioid and giant cells (hematoxylin and eosin, ×76).

These authors comment that "The initial acute response, characterized by PMN proliferation, probably represents activation of the acute inflammatory pathway, while the late granulomatous reaction indicates inflammation produced by a particulate stimulus."

The corneal tissue became available for study seven months after isobutyl-2-cyanoacrylate had been applied to the corneal perforation in the patient we have reported. A granulomatous response to the cyanoacrylate was a striking feature (foreign-body giant cells had enveloped the fragments of plastic). No other foreign bodies were present, nor was any other cause for a granulomatous reaction demonstrable.

Another aspect of corneal tissue reaction to the different cyanoacrylates is the dose-related nature of the response observed by various investigators. In our laboratory we created lamellar pockets in six rabbit corneas and immediately thereafter injected a small amount of isobutyl-2-cyanoacrylate monomer into the tract. Pathologic examination seven weeks later showed the corneal incisions to be well healed, without undue scarring. Only a few giant cells surrounding scattered fragments of the plastic were observed. This is in contrast to the striking granulomatous response to innumerable fragments of cyanoacrylate in the presently reported patient. We believe the extensive necrosis in our patient's cornea permitted relatively large amounts of the cyanoacrylate to enter the stroma adjacent to the perforation tract. This resulted in a massive granulomatous response to the plastic, in contrast to the limited reaction observed in clean, surgically created wounds in animals, where necrosis away from the perforation site itself

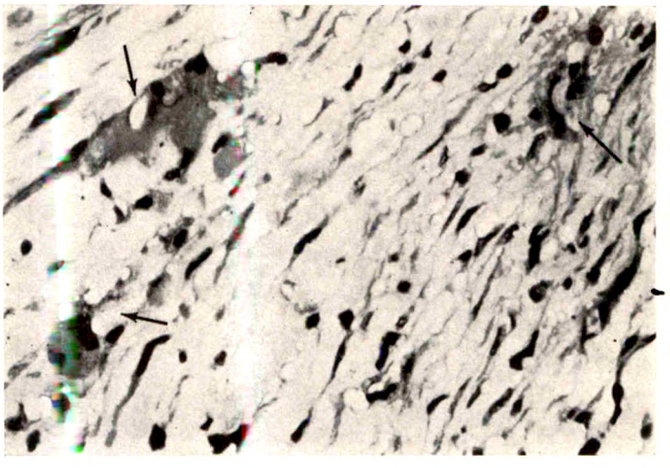


Fig. 5 (Ferry and Barnert). Giant cells and epithelioid cells envelop many of the "clear" spaces representing sites of adhesive deposition (arrows) (hematoxylin and eosin, ×480).

was minimal. Perhaps a more vigorous curettage and removal of necrotic corneal tissue before application of the adhesive to our patient's perforation site would have resulted in a less extensive deposition of cyanoacrylate in his cornea.

Sealing certain corneal perforations with tissue adhesive is a therapeutic method of considerable promise. Webster and associates,[15] and Malaev,[16] have reviewed some advantages inherent in this technique. In the presently reported patient there was widespread corneal necrosis and softening in addition to the localized perforation. Under these circumstances we were most reluctant to perform an immediate keratoplasty and elected to attempt closing the perforation with cyanoacrylate adhesive. The successful sealing of the perforation permitted subsequent penetrating keratoplasty at a time when the cornea was no longer as soft and necrotic. Another major feature of this technique is that if the corneal perforation is located peripherally, scarring consequent to wound healing may not interfere with corneal transparency along the visual axis, and the patient may be spared a surgical procedure.

## Summary

When isobutyl-2-cyanoacrylate adhesive was used to close an area of perforation in an extensively necrotic cornea, the plastic produced a marked granulomatous keratitis. This was not the response observed in animal experiments; seven weeks after the same material was injected in six rabbit corneas, pathologic examination showed the corneal incisions in these animals to be well healed and without undue scarring. In the patient reported, it is probable that extensive necrosis permitted relatively large amounts of the cyanoacrylate to enter the stroma. Despite this patient's reaction to the adhesive, the use of the cyanoacrylate permitted the successful sealing of the perforation and allowed subsequent penetrating keratoplasty to be performed when the cornea was no longer as soft and necrotic. This technique of using cyanoacrylate adhesive is of potential value in sealing certain types of corneal perforations.

### Acknowledgments

We thank Mrs. Lina Rey for technical assistance and Mr. Don Wong for the clinical photographs.

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# UNUSUAL EPITHELIAL CHANGES IN A CASE OF COMBINED CORNEAL DYSTROPHY OF FUCHS

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In 1910, Fuchs described a degenerative disease of the cornea involving first the endothelium and then the epithelium.[1] This combined endothelial–epithelial dystrophy of Fuchs (Fuchs' dystrophy) is characterized by early endothelial guttata and later by stromal edema and epithelial vesicles.[2] The degenerative changes are progressive and lead to corneal opacity. Since corneal homografts may be used to correct the opacity, fresh corneal specimens are thus available postoperatively for light and electron microscopic observations. Ultrastructural studies are helpful in understanding the degenerative changes; however, these studies have concentrated on presenting details of fibrillar changes in Descemet's membrane and stroma.[3,4] The present study describes unusual changes in the epithelium in a case of Fuchs' dystrophy.

The intracellular and intercellular edema of the deepest layer of the epithelium and the structure of the vesicles were described by earlier investigators.[2] In 1958, Chi noted subepithelial fibrillar material in several cases studied by light microscopy.[5] In 1967, McTigue reported a case with delicate fibrillar material containing "invading cells" which he considered to migrate from the superficial corneal stroma to lie beneath the basement membrane of the epithelium.[6] The fibrillar layer in the present case is shown to lie above the epithelial basement membrane and the epithelial cell layers are traversed and encapsulated by septa of fibrillar material which is continuous with the subepithelial fibrillar material.

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## CASE REPORT

A 56-year-old white man gave a history of blurring of vision and intermittent pain in the right eye for one year. He had had an uneventful cataract extraction in the right eye three years previously. On initial examination, the visual acuity was 20/100 in the right eye and 20/30 in the left eye with correction. There were guttate changes involving at least 40% of the endothelial surface of the right eye with the vitreous face touching the endothelium. Corneal edema was present but no vesicles or bullae were observed. The left eye showed central guttata and an early senile cataract. Applanation tonometry was 17 mm Hg in each eye. Pain in the right eye increased and the visual acuity decreased to 20/400 at which time a 7.5 mm penetrating homograft with vitrectomy was performed with good visual result.

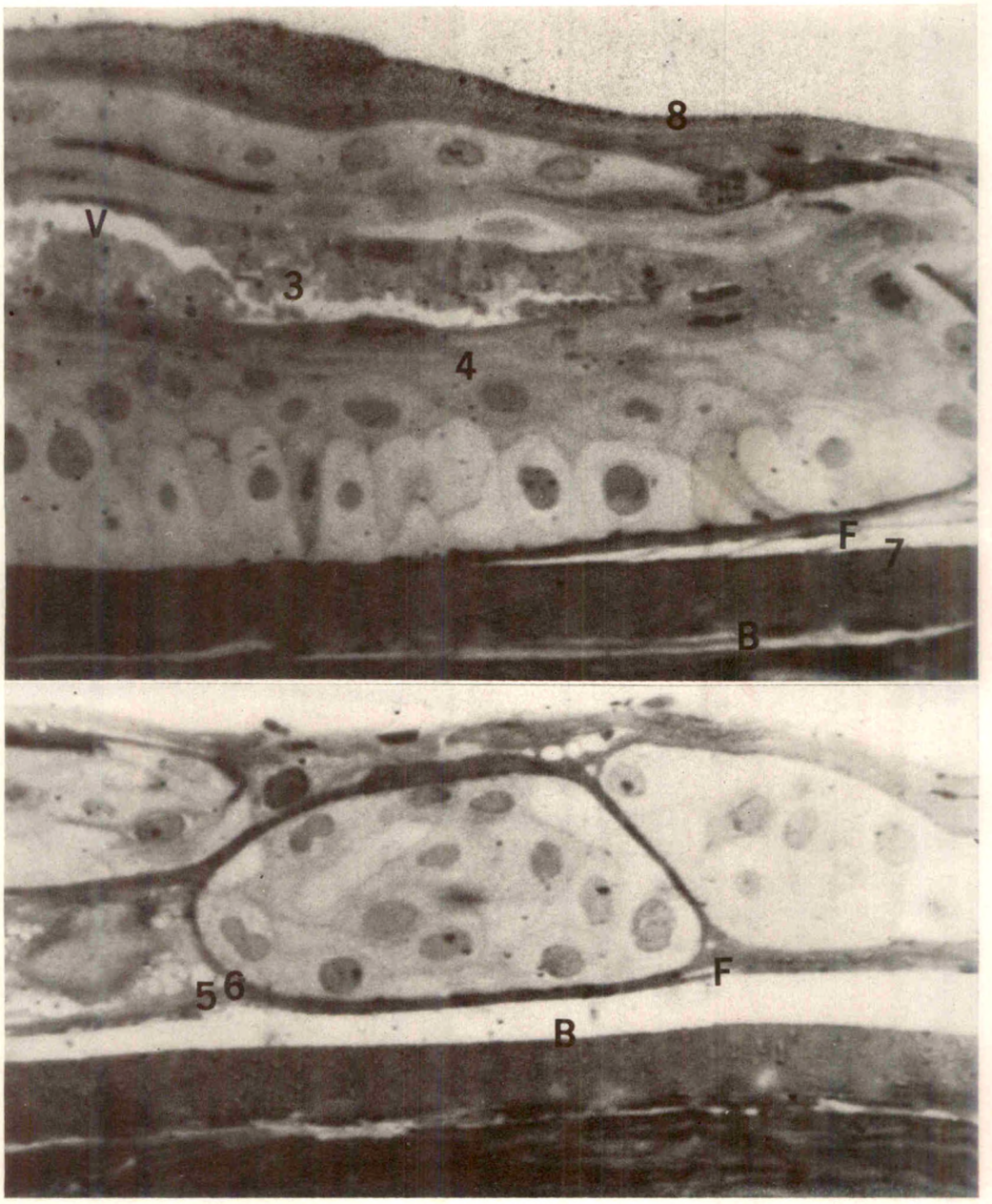
## MATERIAL AND METHODS

The removed corneal button was fixed in freshly prepared 4% formaldehyde, then dehydrated through increasing concentrations of methanol and propylene oxide and embedded in Araldite. The tissues were cut through the center of the cornea into four equal parts. Thick sections were stained with 0.1% toluidine blue in 1% borax solution. Thin sections were stained with uranyl acetate and lead citrate for electron microscopic studies.

## RESULTS

The epithelial vesicles in this case gave the appearance of being blood vessels under light microscopy (Figs. 1, 2). At higher magnifications the vesicles were found to contain degenerating epithelial cells and cellular debris (Figs. 3, 4). The individual epithelial cells are attached to each other by desmosomes (Fig. 4). The vesicles appear to result from the encapsulation of groups of epithelial cells by the fibrous sheets (Fig. 2).

The fibrillar layer covering groups of epithelial cells morphologically resembles Bowman's layer in structure (Figs. 5-8). Fine fibrils and short collagen fibers are intermingled and randomly oriented (Fig. 7). However, this fibrillar layer does not appear to be an extension of Bowman's layer since it is




Figs. 1 and 2 (Schroeder and Hanna). Photomicrographs of the epithelium (a central and a peripheral area) in Fuchs' dystrophy. The epithelium is divided into numerous groups of cells by a fibrillar layer (F) that lies above Bowman's membrane (B). A portion of an intraepithelial vesicle (V) is seen in Figure 1 (top), while the numbers in both illustrations correspond to the figure numbers of subsequent illustrations showing these same sites as they appear on electron microscopy (toluidine blue, ×600).

well above and separated from this layer by the basement membrane of the epithelial cells (Fig. 5). The epithelial cells are attached to the fibrillar layer by hemidesmosomes, while in no case were the epithelial cells observed to be attached to Bowman's layer by cell junctions. Cells resembling keratocytes are occasionally found in the fibrillar layer sur-

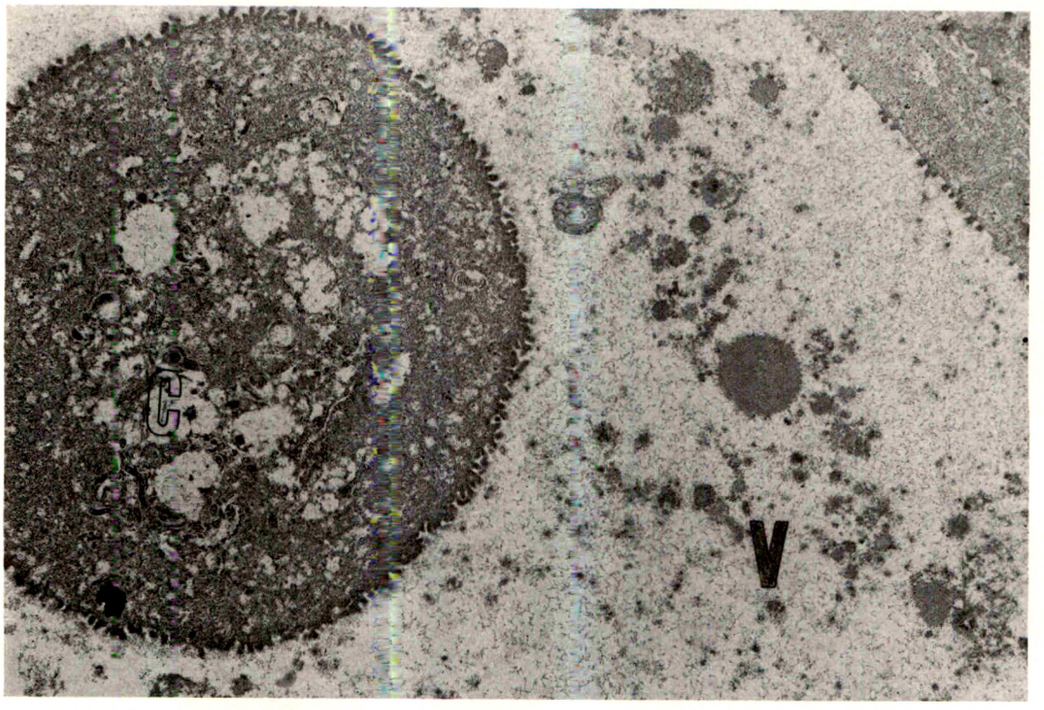



Fig. 3 (Schroeder and Hanna). Electronmicrograph of a cross-section of the vesicle (V) containing a degenerating cell (C) and other cellular debris (×9000).

rounding the epithelium (Figs. 5, 7). The fibrillar layer is continuous with the anterior surface of the cornea (Figs. 1, 2). The surface fibrillar layer is shown being exfoliated from the corneal surface (Fig. 8). Neovascularization and evidence of inflammatory processes are absent from the corneal button.

When four other corneal buttons (surgical specimens from additional cases of Fuchs' dystrophy) were examined in this laboratory, each demonstrated corneal changes that were typical of those previously reported. In each case, a collagen-like fibrillar layer was found between Bowman's layer and the basal epithelial cells. Occasionally, the fibrillar layer extended between basal epithelial cells. The fibrillar layer generally resembled Bowman's layer in structure rather than fibers of the stroma.

## Discussion

Previous reports of the pathologic changes at the ultrastructural level in Fuchs' dystrophy have stressed the stromal and endothelial changes. A few reports have described the presence of subepithelial fibrillar material located below the basal epithelial cells.[3,5,6] The present report describes the complete encasement of the epithelium by a collagen fibrillar layer containing fibroblasts. The keratocytes were surrounded by short collagen-like fibrils which are arranged randomly in a structure morphologically identical to Bowman's layer. Since the changes of Fuchs' dystrophy occur in adults, this leaves little doubt that keratocytes are capable of producing a Bowman-like layer under this pathologic condition in the adult eye. Previous studies have indicated that Bowman's layer is formed only during embryonic life. In the case of Fuchs' dystrophy a new Bowman's layer may form.

## Summary

In a case of Fuchs' combined corneal dystrophy, an unusual epithelial change was seen upon microscopic examination of the diseased corneal button after surgery. The

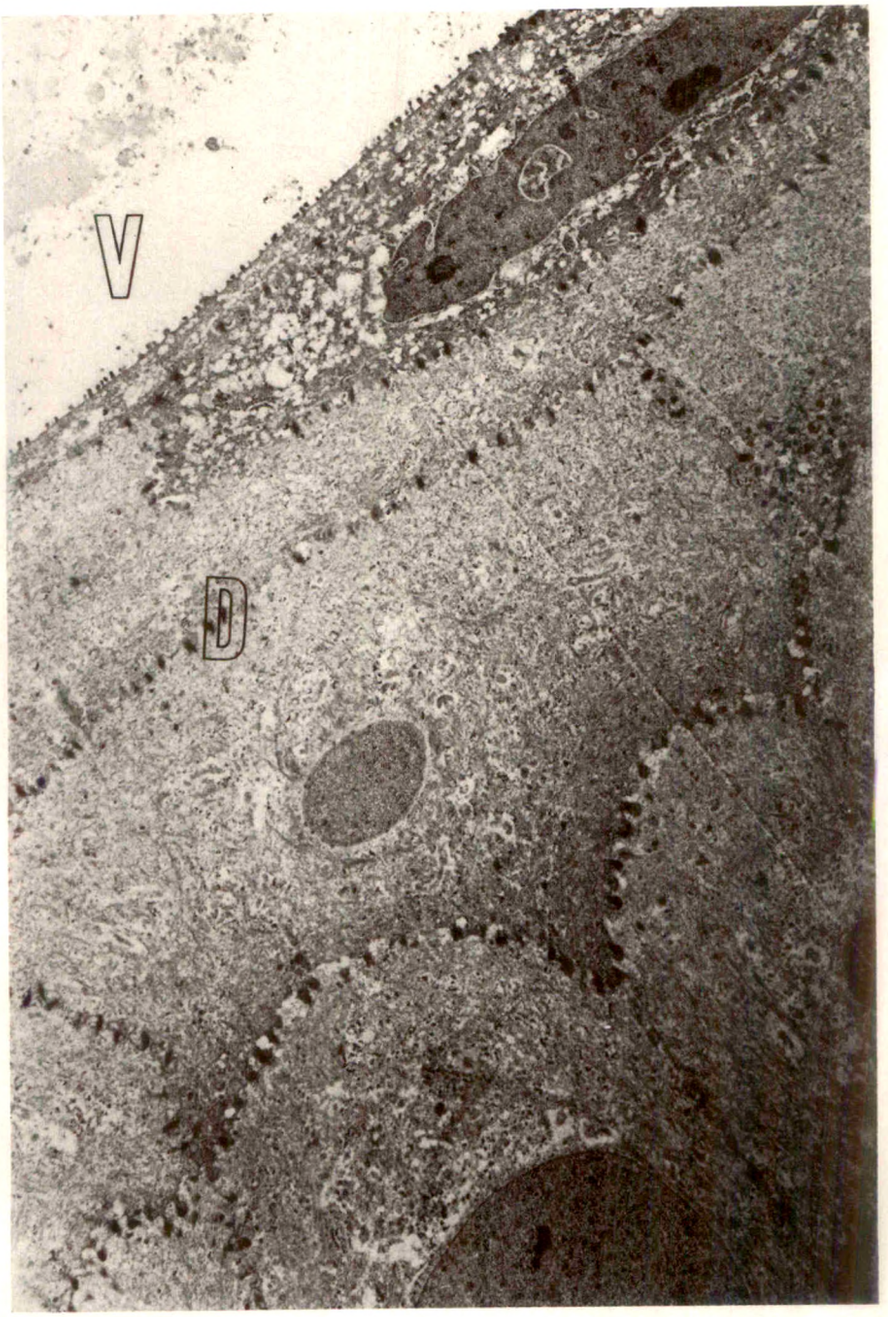



Fig. 4 (Schroeder and Hanna). View of the cells lying deep to the vesicle (V). Desmosome junctions are demonstrated (D). Note the relative lack of intracellular organelles in these epithelial cells (×9000).

epithelium was separated into encapsulated islands by a collagen fibrillar layer that resembled Bowman's layer in structure. These fibrils were apparently produced by keratocytes located above Bowman's layer and this suggests that under certain conditions a new Bowman-like layer may be produced in adults, despite the fact that it is presently accepted to be formed only during embryonic life.

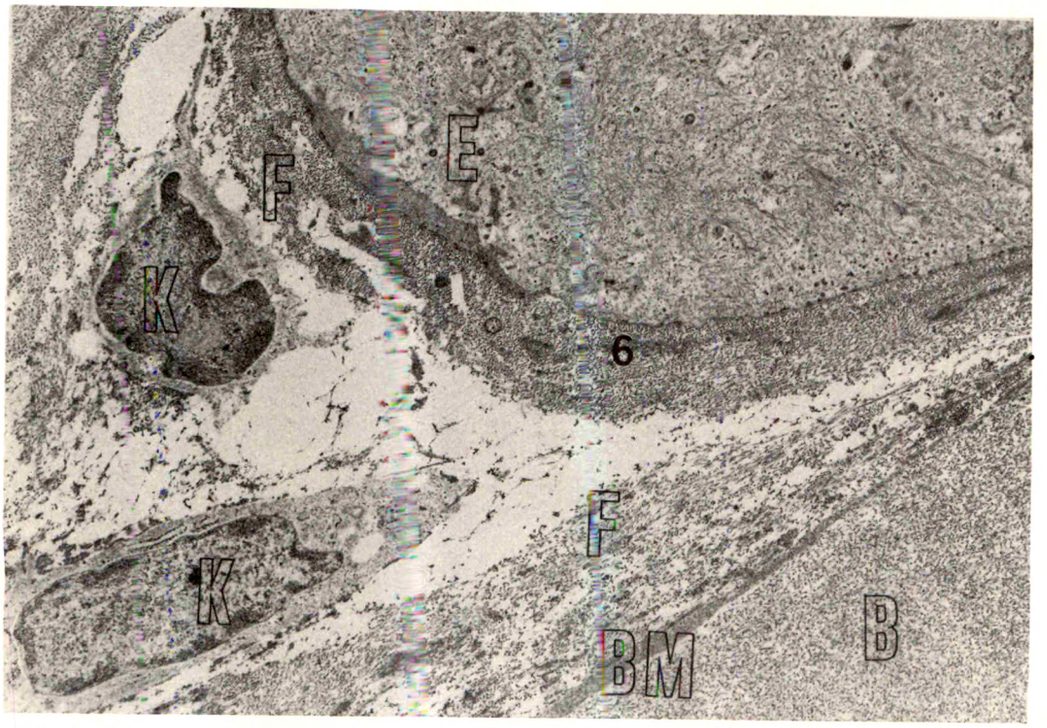



Fig. 5 (Schroeder and Hanna). The fibrillar layer (F) surrounding the epithelial cells (E) is generally attached to the epithelial cells by hemidesmosomes. The fibrillar layer resembles Bowman's layer, based on the appearance of the macroperiod of collagen in closely packed bundles. This resemblance is especially apparent in Figure 7. At the junction between the groups of epithelial cells (E) are found cells (K) surrounded by the fibrillar layer which is generally separated from Bowman's layer (B) by a basement membrane (BM). The 6 refers to the area enlarged for Figure 6 (×6000).

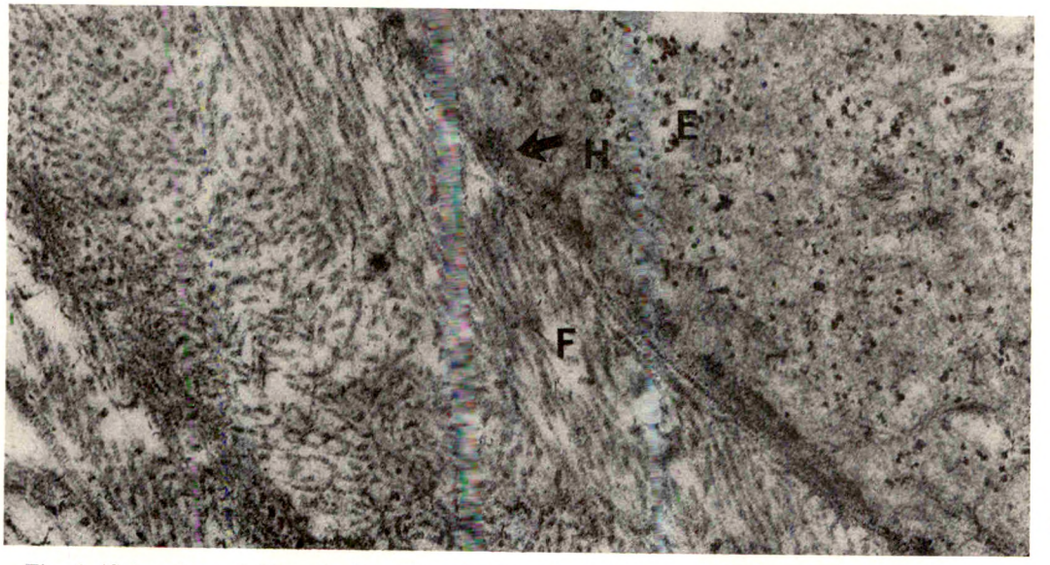



Fig. 6 (Schroeder and Hanna). An enlarged view of area 6 shown in Figure 5 showing the collagenous nature of the fibrillar layer and the hemidesmosomes (H) of an adjacent epithelial (E) cell (×25,000).

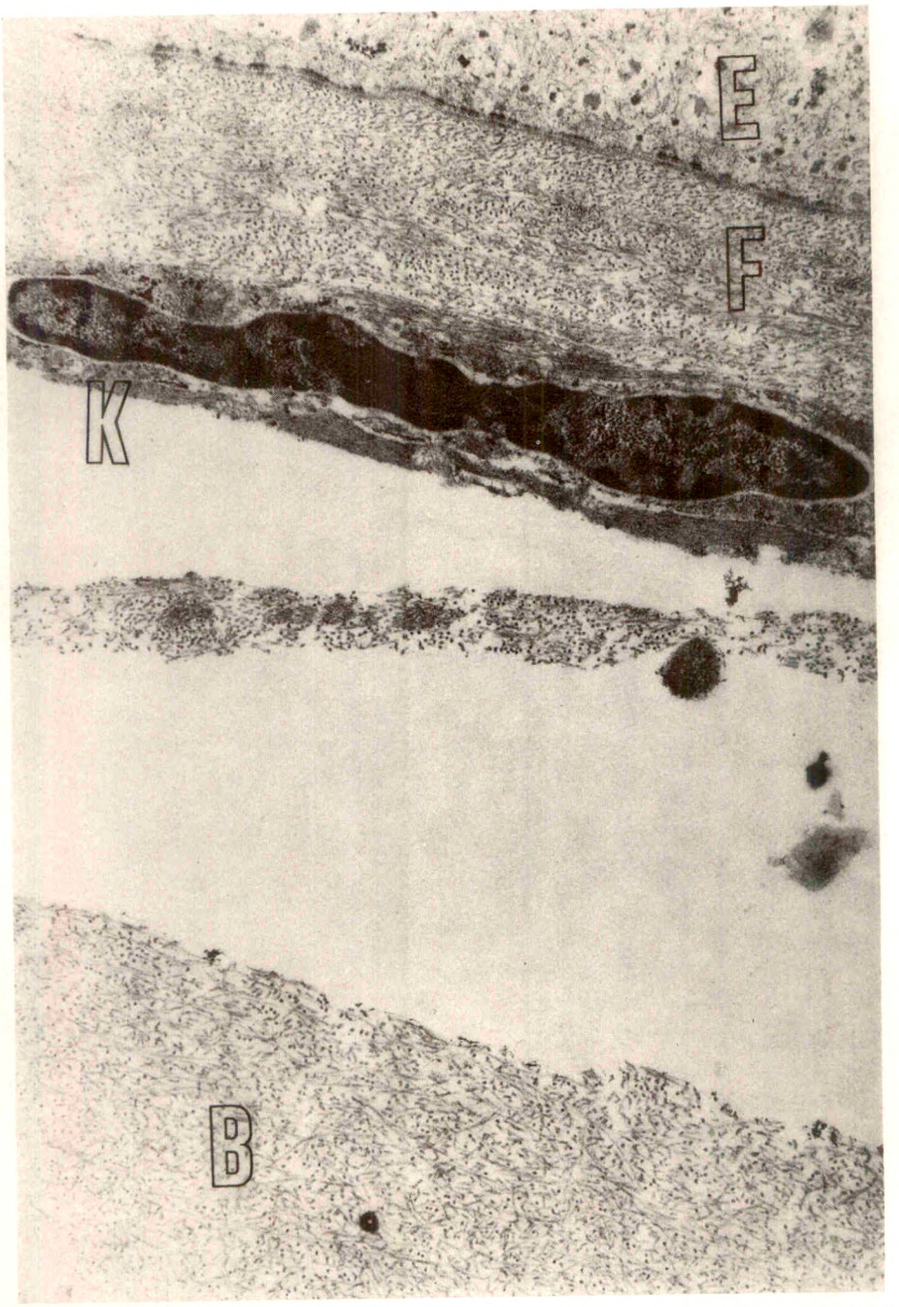



Fig. 7 (Schroeder and Hanna). In many areas, the fibrillar layer is separated from Bowman's layer (B). Occasionally, the fibrillar layer contains cells that closely resemble keratocytes (K) in structure (×30,000).




Fig. 8 (Schroeder and Hanna). The fibrillar layer extends to the anterior surface of the cornea where, in association with cellular debris, it defoliates (×10,000).

ACKNOWLEDGMENTS

We thank Catherine Dodd for her considerable assistance in the electron microscopic observations and F. T. Fraunfelder and D. Van Horn, who supplied the corneal buttons.

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# THE ULTRASTRUCTURE OF REIS-BÜCKLERS' DYSTROPHY

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In 1949, Bücklers[1] described a corneal dystrophy affecting four successive generations of a German family, some members of which had already been reported by Reis[2] (1917). These authors stated that this condition is characterized clinically by a diffuse opacification in the region of Bowman's membrane and recurrent epithelial erosions. Since then, various studies have described the clinical and histopathologic features of this dystrophy. The first electron microscopical study was reported by Griffith and Fine[3] (1967). They studied the scrapings from the superficial portion of a cornea with the clinical appearance of the dystrophy. The specimen showed normal appearing epithelial cells, but the basement membrane of the epithelium appeared poorly defined or absent. Bowman's layer was almost replaced by collagen fibrils. Masses of closely packed, delicate fibrils were found in the junctional areas between Bowman's membrane and the adjacent stroma and were thought to be fibrillar degeneration. There was insufficient stroma for a definitive description. Later, Rice and associates[4] (1968) described the clinical, genetic, histological, and electron microscopic appearances of two corneas with Reis-Bücklers' dystrophy. Electron microscopy amplified the report of Griffith and Fine, and in addition showed that the epithelium was degenerated, particularly in the basal layer where there were also clusters of extremely electron-dense cells ("dark cells"). This study was almost identical to that of Griffith and Fine—i.e., Bowman's membrane was replaced by a fibrous tissue consisting of disoriented collagen fibrils of varying electron density interspersed with electron dense fibrils of smaller caliber (about 8.0 nm) which were occasionally grouped in irregular masses. In addition, the anterior stroma was examined and showed active fibroblasts. This indicated that the changes in Bowman's layer were regenerative rather than degenerative.

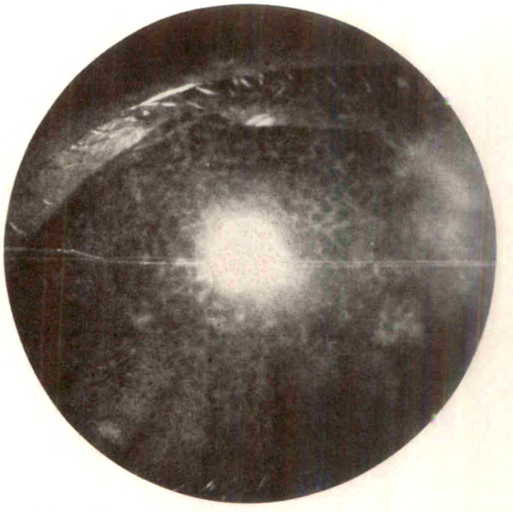


Fig. 1 (Akiya and Brown). Preoperative appearance of right cornea is typical for Reis-Bücklers' dystrophy.

This paper is the third of the electron microscopy of Reis-Bücklers' dystrophy and the second of a full-thickness corneal button.

## MATERIALS AND METHODS

The material for this study consisted of a corneal disk removed during keratoplasty. The patient was an 18-year-old woman with a history of recurrent erosions in both eyes for more than 10 years. The visual acuity was reduced to RE: 20/80 and LE: 20/30. Slit lamp examination showed a ground glass appearing opacification of the subepithelial area of both corneas (Fig. 1). The peripheral cornea was spared. The patient's mother had a similar history and had similar

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corneal opacifications which were more dense.

The corneal disk removed at surgery was bisected immediately after removal from the patient. One-half was fixed in 10% neutral formalin, embedded in paraffin, and stained with hematoxylin and eosin, periodic acid Schiff reagent, toluidin blue, colloidal iron, and Congo red. The other half was fixed in 3% glutaraldehyde in 0.2% sodium cacodylate buffer (pH 7.4) and postfixed 2% osmium tetroxide in 0.2M sodium cacodylate and embedded in Epon.

Thin sections were cut on a LKB-3 microtome with a diamond knife, mounted on uncoated copper grids, stained with uranyl acetate and lead citrate, and examined with a Siemans Elimiscop 1A at 80 kv. Thicker sections (5μ) of the epoxy-embedded tissue were stained with either toluidin blue or basic fuschin and alkalinized methylene blue[5] and examined with the light microscope.

### Histology

The epithelium was irregular in thickness. The basal layer of the epithelium had many pale swollen cells, many darkly staining cells, and intercellular vacuoles. The nuclei of the pale cells had irregular outlines and were degenerative. Bowman's membrane was almost entirely replaced by a material or deposit which stained bright red with basic fuschin and alkalinized methylene blue (Fig. 2). Similar material could be seen in the superficial stroma (Fig. 2). These areas did not stain with PAS, colloidal iron, or Congo red, but was faintly red with Masson's stain.

### Ultrastructure

The cellular degenerative changes—i.e., swollen mitochondria, large vacuoles, swelling and disruption of the endoplasmic reticulum—were evident through all layers of the epithelium. There was distention of the intercellular spaces and the desmosomes were

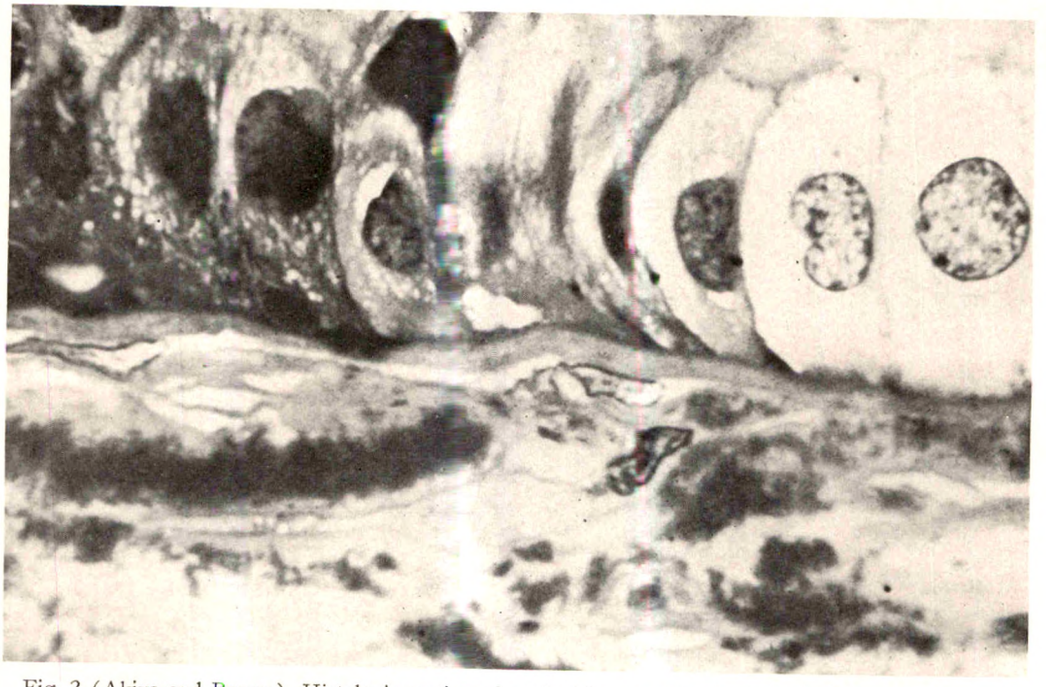


Fig. 2 (Akiya and Brown). Histologic section of excised host cornea shows both dark and pale swollen basal epithelial cells. Superficial stroma has stained darkly and it shows somewhat amorphous deposits (basic fuschin and alkalinized methylene blue, ×400).

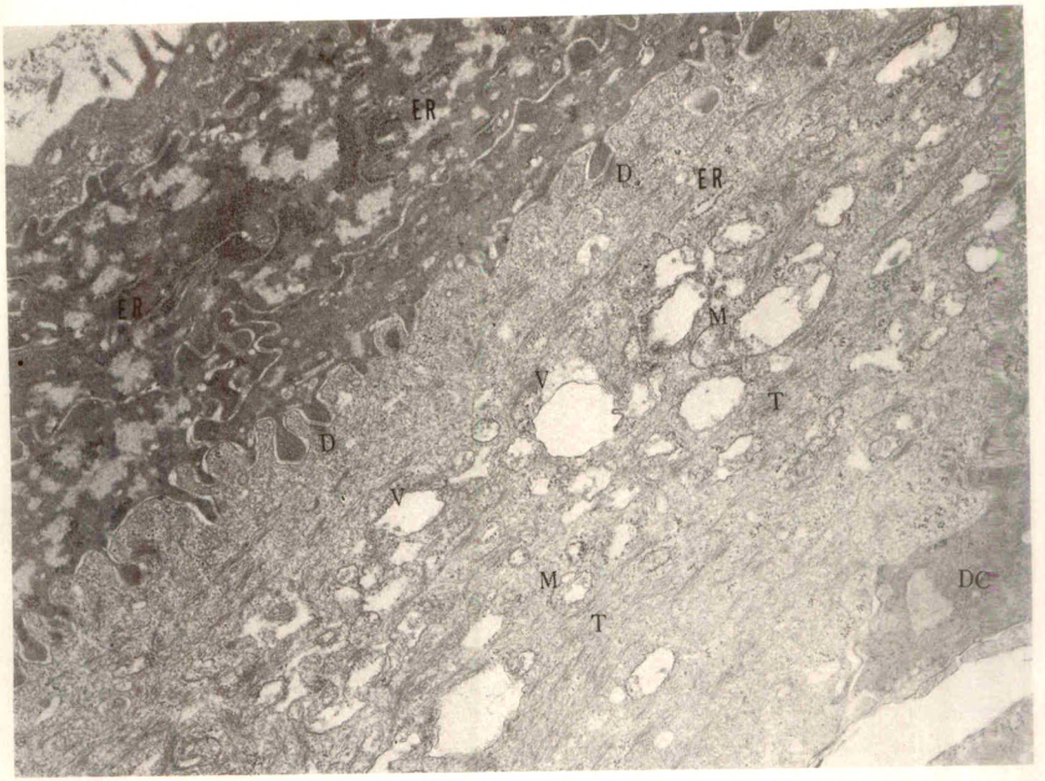



Fig. 3 (Akiya and Brown). Electron micrograph of basal epithelial cells. Both the electron-dense cell (DC) and the adjacent lighter cells have few recognizable organelles except for swollen mitochondria (D = desmosome, M = mitochondria). In the intercellular space, there is an extension of another dark cell (×17,000).

normal. Prominent in the basal layer were groups of cells which were extremely electron dense and flat or polymorphous in shape. These "dark cells" also showed degenerative changes and in some the internal structures were indiscernable. The basement membrane was irregularly present and where it was absent, the epithelium was usually detached from the underlying stroma.

Under low magnification, Bowman's membrane appeared to be replaced by an unorganized fibrous tissue containing collagen fibrils and electron-dense, finely granulated deposits. Under higher magnification these deposits were seen to be made up of fibrils with diameters of 5.0-8.0 nm (Figs. 4-6).

There were many keratocytes in this abnormal Bowman's layer. They appeared to be either degenerating, grossly degenerated with cell membrane breakdown, or active, as suggested by the increase in number and size of the rough-surfaced endoplasmic reticulum (Fig. 6). The endoplasmic reticulum in these active appearing cells contained fine filaments or finely granulated substances in their cisternae.

## Comments

The electron microscopic examinations of the specimen of Reis-Bücklers' dystrophy reported in this paper are almost identical to those of Rice and associates.[4] There were two main alterations. The first was degenerative changes of almost every epithelial cell, but especially the basal cells. The second was that Bowman's membrane was completely absent and replaced by masses of disoriented collagen fibrils and smaller electron-dense

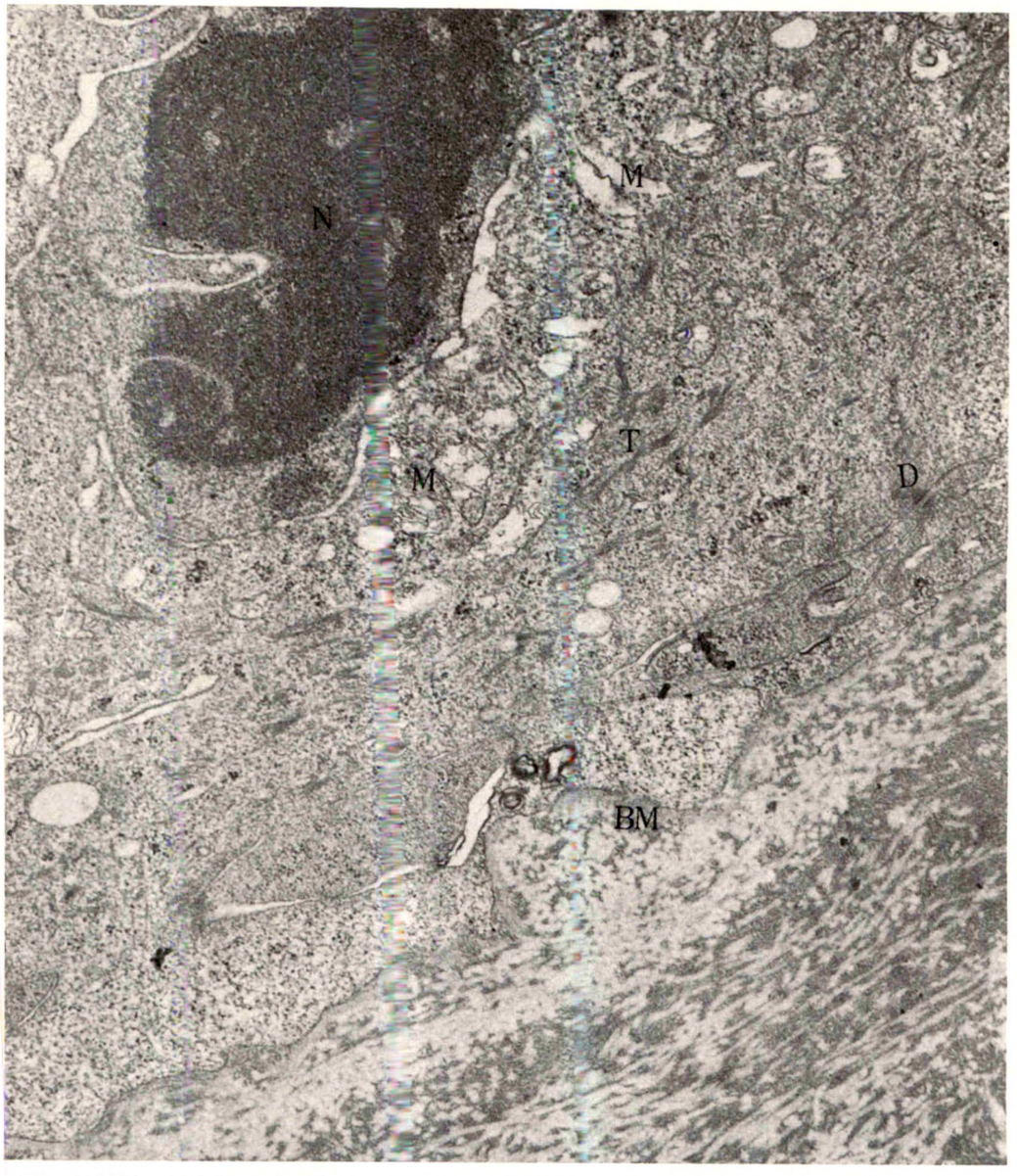



Fig. 4 (Akiya and Brown). The basal cell membrane is very irregular, and portions of the basement membrane (BM) are present. Bowman's membrane is replaced by the electron-dense fibrous materials (M = mitochondria, N = nucleus, D = desmosome, T = intracytoplasmic fibril) (×17,000).

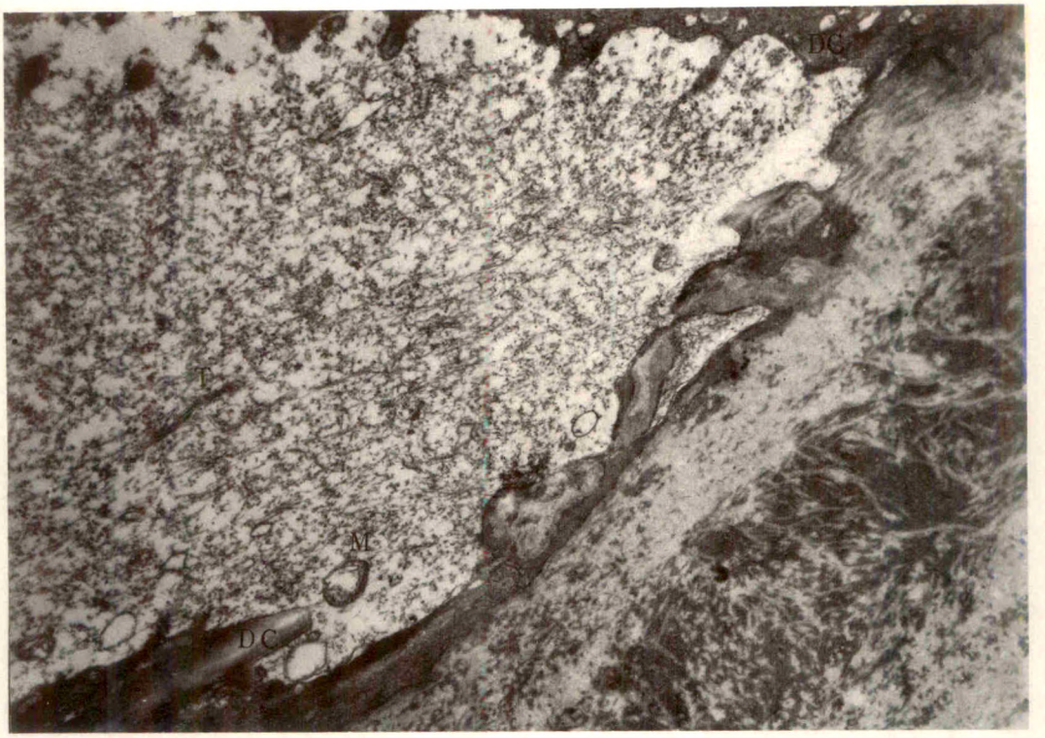



Fig. 5 (Akiya and Brown). This micrograph shows two basal epithelial cells and the anterior stroma. The basal membrane is absent. Bowman's membrane is replaced by disorganized tissues containing electron-dense masses which surround irregular extensions of one of the basal cells (×17,000).

fibrils whose composition and origin have not been determined. Similar material was unevenly dispersed in the anterior stroma near active fibroblasts.

The most likely origin of the new fibrous tissue is the corneal stromal fibroblast. A less obvious origin is the epithelial cell which under normal conditions produces tropocollagen or a collagen-like protein which is incorporated into the epithelial basement membrane. The consistently intimate relationship between the predominantly collagenous tissue which replaced Bowman's layer and the epithelium suggests that the new tissue could be a product of altered epithelial metabolism.

The abnormal stromal deposits in the specimen of Reis-Bücklers' dystrophy stain bright red with basic fuschin and alkalinized methylene blue. Generally, these deposits do not stain with other methods and it may be that this stain will be useful in the localization and identification of the deposits of Reis-Bücklers' dystrophy.

## Summary

The ultrastructural changes of Reis-Bücklers' dystrophy were mainly epithelial cell degeneration and replacement of Bowman's membrane by masses of collagen fibrils. Because these changes are identical to those reported previously, it is probable that they are specific for the dystrophy. The anterior stromal deposits may be visualized histologically after staining with basic fuschin and alkalinized methylene blue.

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Fig. 6 (Akiya and Brown). This is a section through the anterior stroma showing fibrillar deposits extending beyond Bowman's zone and surrounding a stromal cell with well-developed rough surfaced endoplasmic reticulum (ER). Mitochondria (M) are normal. Basal portion of a basal epithelial cells is in left corner of photograph (×14,000).

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# OCCURRENCE OF HERPES ZOSTER OPHTHALMICUS IN A CHILD WITH ABSENT IMMUNOGLOBULIN A AND DEFICIENCY OF DELAYED HYPERSENSITIVITY

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The following case is reported to present the uncommon finding of herpes zoster ophthalmicus in a child, and to show its possible relationship to an immunologic deficiency.

## CASE REPORT

A seven-year-old white boy was seen in the ophthalmology clinic on January 12, 1970, with a three-day history of a rash on his left forehead. Examination at that time revealed a skin eruption typical of herpes zoster ophthalmicus. It was noted that there was involvement of the skin of the inner canthus and the tip of the nose. Except for mild conjunctival injection, there was no evidence of any ocular involvement. Uncorrected visual acuity was 20/25 in each eye. Neosporin ophthalmic solution was instilled and examination the following day showed a small amount of edema of the lower eyelid.

Three days later, the uncorrected visual acuity in the left eye had decreased to 20/60. There was epithelial edema of the cornea and an irregular fluorescein staining pattern near the limbus. The stroma was not involved. There was a moderate aqueous flare and a few small, nonpigmented keratic precipitates (KPs) present. Atropine ophthalmic solution was begun. The following day the patient was febrile and dehydrated, and he was admitted to the hospital. Topical atropine and neosporin were continued, but five days later the aqueous flare in the anterior chamber was more severe, many more KPs were present, and there were folds in Descemet's membrane. Topical prednisone 1% was added to the local medications. Two days later, the aqueous flare was much less severe and there were fewer KPs. The central portion of the cornea revealed a superficial irregular stain measuring approximately 5.0 mm in diameter. At this time, the corticosteroid drops were decreased to twice a day. Three days later, the stain of the corneal epithelium was the same; however, the signs of anterior uveitis were less and the topical corticosteroids were then discontinued.

Three weeks later, an irregular central punctate stain of the corneal epithelium remained, several mid-peripheral, subepithelial corneal opacities were present, and corneal sensation was decreased. The patient was then put on methylcellulose drops four times a day. Two months later a tarsorrhaphy was performed due to persistent, diffuse corneal staining associated with decreased corneal sensation. It is also notable that there was an absence of lymphoid follicles in the conjunctival cul-de-sac, a finding described in immunoglobulin deficiencies by Little and Schulkind.[1]



FIG. 1 (Kielar, Cunningham, and Gerson). Cutaneous eruption seen on initial examination.

This child has had generalized candidiasis involving the mucous membranes of his mouth, skin, and nails since early infancy. The total leukocyte count and differential have been normal. His serum immunoglobulins were normal at the age of 18 months, but the serum, tear, and salivary IgA gradually diminished and have not been detectable since the age of six years. The serum IgG and IgM are normal for his age. The boy has consistently had a negative response to candida skin tests as well as to a variety of other tests for delayed hypersensitivity. It is of note that this patient had varicella at two

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and one-half years of age and other illnesses with a usual course.

## Discussion

It is known that herpes zoster may be associated with gamma globulin deficiency. In a large pediatric hospital, Keidan and Mainwaring[2] observed 17 cases of herpes zoster involving various cutaneous sensory nerves during a 14-year period, and several of these patients had decreased serum gamma globulin levels when the rash appeared. Unfortunately, serum IgA levels were not reported on these patients.

There is a frequent association of herpes zoster and chronic lymphatic leukemia and Hodgkin's disease, and these lymphomatous diseases may have associated decreased gamma globulin levels. Shanbrum, Miller, and Haar[3] postulated that the decreased gamma globulin antibodies make these patients more susceptible to virus infection, and this decrease may also explain the tendency for herpes zoster to become generalized in these patients. Miller[4] has shown that patients with lymphomas have decreased tuberculin-type sensitivity, and decreased circulating antibodies. In a similar manner, Sokal and Firat[5] have shown that a number of patients with Hodgkin's disease and herpes zoster have a negative delayed type skin test to numerous and various antigens.

There is evidence that IgA deficiency is associated with several diseases. It is known that IgA antibodies have viral neutralizing activity.[6] Chilgren, Meuwissen, Quie, and Hong[7] have described several cases of chronic mucocutaneous candidiasis with inability of these patients to manifest delayed hypersensitivity, and also demonstrated in these patients the presence of a defect in parotid fluid IgA antibody against C. albicans. Patients with ataxia-telangiectasia have been shown to have low IgA levels, absent delayed hypersensitivity reactions, and progressive sinobronchial pulmonary infections.[8] Tokumaru[9] also demonstrated decreased herpes simplex IgA antibody titers in the serum of patients with recurrent herpetic stomatitis.

Although there is no direct evidence for the association of herpes zoster in chiddren with IgA deficiency, the occurrence of these two uncommon findings in a child may be more than a fortuitous association. Herpes zoster occurs in lymphomatous neoplasias where there is evidence of an altered immune mechanism, including absent delayed hypersensitivity. IgA deficiency also occurs in disease states where there are defects in delayed hypersensitivity. There is an association of lymphoid tumors in patients with ataxia-telangiectasia, which manifests IgA deficiency and absent delayed hypersensitivity as its immunologic defects.[10] The prolonged and severe course of herpes zoster ophthalmicus in this child is likely to be related to the absence of secretory and serum IgA together with a deficiency of delayed hypersensitivity.

## Summary

In a seven-year-old boy with an IgA deficiency, the course of herpes zoster was prolonged and severe. This child's history showed that serum immunoglobulins were normal at the age of 18 months; however, the serum, lacrimal, and salivary IgA were no longer detectable after the age of six years. Normal conjunctival lymph follicles were absent. It is postulated that the IgA deficiency and absent delayed hypersensitivity increased the susceptibility to, and prolonged the clinical course of the viral illness in this child.

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OPHTHALMIC MINIATURE

Once we were hunting under the isolated rocks of La Cassidaigne. Twenty fathoms down Did shot an eight-pound liche. The harpoon entered behind the head but missed the spinal column. . . . Dumas hauled in the last feet of cord and got a grip on the harpoon shaft. He flashed his belt dagger and plunged it into the heart of the big fish. A thick puff of blood stained the water.

The *blood was green!* Stupefied by the sight, I swam close and stared at the mortal stream pumping from the heart. It was the colour of emeralds. We had swum among the liches as aqualungers, and taken them on goggle-dives, but we never knew there was a type with green blood. Flourishing his astounding trophy on the harpoon Did led the way to the surface. At 55 feet the blood turned dark brown. At 20 feet it was pink. On the surface it flowed red.

Once I cut may own hand seriously 150 feet down and saw my own blood flow green . . . I thought of the liche and managed to convince myself that my blood was really red.

J. Y. Cousteau
*The Silent World*
London, Hamish Hamilton, 1953

# IMMUNOGLOBULIN E IN HUMAN TEARS

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Immunoglobulin E (IgE) is a distinct immunoglobulin class present in serum in extremely low concentrations ranging from 100 to 700 ng/ml.[1,2] It is composed of two light and two heavy chains,[3] possesses antibody activity, and is specifically characterized by the presence of the epsilon antigenic focus on the heavy chains.[1,2]

IgE is of unique importance, as it is the only immunoglobulin that has been isolated and demonstrated to be capable of mediating atopic (reaginic) type hypersensitivity reactions in man. The term reagin was originally applied to the serum factor which on passive transfer to healthy individuals caused allergic symptoms and positive skin reactions (wheal and erythema) to develop. Recent studies demonstrated that a very small amount of IgE antibodies isolated from ragweed-sensitive patients' sera passively sensitizes the skin of normal individuals on intracutaneous injection.[2,4] On challenging the same skin site by the intracutaneous injection of ragweed antigen, a wheal and erythema reaction (Prausnitz-Küstner reaction) occurs.[2,4] The minimum amount of IgE antibody necessary to passively sensitize the skin has been estimated to be on the order of $10^{-6}$ to $10^{-5}$ microgram protein nitrogen.[5]

Extensive studies have shown that the ability of serum immunoglobulin fractions to produce the wheal and erythema reaction is related to the IgE content of the serum fractions studied, and is not associated with the four other known immunoglobulins, IgG, IgA, IgM, and IgD.[4] The IgE fraction of patients' sera which did not contain detectable IgG, IgA, IgM, or IgD demonstrated very high reaginic activity which was removed by anti-IgE but not by specific antibody to the other immunoglobulins.[2,4]

Lymphoid cells producing IgE have been located in the respiratory and gastrointestinal mucosa, and in lymph nodes draining the respiratory tract and gut, but only infrequently in subcutaneous lymph nodes, spleen, buffy coat cells, and marrow.[6] This demonstration of an anatomical association of cells that produce IgE with mucous membranes, combined with the finding of higher ratios of IgE/IgG in sputum and nasal washings compared to the sera of the same individuals, supports the possibility that IgE is produced locally near the mucous membrane surfaces.[7]

It is apparent that IgE, if present in tears, might represent a local immune system participating in atopic phenomena in the eye. Therefore, it was considered important to initially determine the presence of IgE in the tears of normal individuals and patients with presumed atopic disorders (vernal conjunctivitis and hay fever conjunctivitis), using a semiquantitative radioimmunodiffusion technique[8] capable of detecting IgE at levels on the order of $10^{-8}$ g/ml.

## MATERIALS AND METHODS

*Subjects*—Tear samples were obtained from 15 individuals, ages 18 to 40 years, whose ocular histories and external eye examinations were normal. Additional samples were obtained from five patients with untreated, clinically diagnosed, typical vernal conjunctivitis; four patients with untreated active ragweed conjunctivitis (seen during ragweed season); one patient with chronic untreated, bilateral Mooren's ulcer, and one patient with bullous keratopathy two days following penetrating keratoplasty.

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Tear flow was not stimulated by contact with the eye, but the subjects were asked to stare at a point without blinking. When tears began to flow, the first 50 λ were collected in a capillary tube and stored in vials at −4°C for less than one month.

*Radioiodination*—Using rabbit antisheep globulin serum, a pure IgG fraction of such serum was obtained by DEAE chromatography according to the method of Levy and Sober.[9] This preparation was then labeled with $^{131}I$, according to the method of McConahey and Dixon.[10]

*Measurement of IgE*—Sheep antihuman IgE and IgE reference standards were obtained from D. Rowe of the World Health Organization. The IgE reference standard contained 10148 ng/ml. This antiserum is specific for the Fc fragment of IgE. Such specificity precludes any cross-reaction with light-chain determinants of other immunoglobulins present in tears. The immunodiffusion plates containing sheep antihuman IgE were prepared according to the method of Rowe.[8] A series of 3 mm holes were cut in the agar and the individual wells were filled with IgE reference standards, tear samples under test, and phosphate-buffered saline (PBS) controls. The plates were then incubated in a moist chamber at 37°C for 48 hours, washed in the cold with PBS for 48 hours, overlaid with the $^{131}I$ rabbit antisheep globulin for 30 minutes, and allowed to stand at room temperature overnight. The excess unreacted $^{131}I$ label was removed by washing with PBS for 48 hours. The plate was dried and exposed to x-ray film for several hours. The diameter of the diffusion ring around the well indicated the relative IgE concentrations (Fig. 1).

*Measurement of IgA*—The IgA content of tear samples was measured by radial immunodiffusion in Hyland plates as previously described.[11]

## Results

IgE was determined in a semiquantitative manner and found in small, detectable amounts in the tears of all patients studied. The IgE determined was total tear IgE and does not selectively demonstrate IgE antibody.

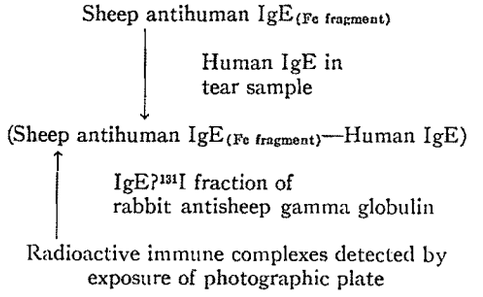



Fig. 1 (Braunninger and Centifanto). Schematic diagram of IgE determination by radioimmunodiffusion method.

It was possible, using a double-blind method, to separate two populations of samples on the basis of relative IgE content. One group demonstrated large immune rings which extended more than 1 mm beyond the rim of the well on the exposed photographic plates, while the other group showed smaller but still definite rings compared to controls. The group of patients whose specimens demonstrated large immune rings had measurable IgE in tears ranging from 1650 to 2600 ng/ml. Specimens from the other group demonstrated smaller but still definite rings that were not quantitatively resolved by our method.

The group demonstrating relatively high IgE levels included seven patients with diseases generally accepted as being caused by atopy and included all five cases of vernal conjunctivitis, two of the four cases of ragweed conjunctivities, and only one of the 15 normal subjects. The group demonstrating minimal IgE included the patient with Mooren's ulcer, the post-keratoplasty patient, the two remaining patients with ragweed conjunctivitis, and 14 of the 15 normal subjects (Table 1).

Simultaneous quantitative IgA determinations on all the tear samples studied were within the range of normality and no corre-

TABLE 1

RELATIVE IgE DETERMINATIONS IN TEARS

| Diagnosis | Age (in years) | Relative IgE Content | Range IgA (mg/100 ml) |
|---|---|---|---|
| Vernal conjunctivitis | 14–29 | Elevated in 5 of 5 | 24–33 |
| Ragweed conjunctivitis | 23–42 | Elevated in 2, trace amount in 2 of 4 | 11.5–20 |
| Penetrating keratoplasty | 46 | Trace amount in 1 of 1 | — |
| Mooren's ulcer | 72 | Trace amount in 1 of 1 | 36 |
| Normal individuals | 16–40 | Elevated in 1 of 15<br>Trace amount in 14 of 15 | 8.8–50 |

lation between IgE and IgA tear content was found. Furthermore, there was no correlation between the clinical inflammatory state of the eye from which the tears were obtained and the relative IgE levels measured. The data indicated that IgE is present in human tears in detectable amounts and strongly suggest an association of higher IgE tear content with atopic disease of the external eye. However, a relatively low tear IgE level does not exclude allergy and elevated IgE in tears may occur without apparent allergic disease. Relatively small amounts of tear IgE were present in two of the four patients with ragweed conjunctivitis, while one of the 15 apparently normal individuals had elevated tear IgE.

## DISCUSSION

The detection of IgE in normal human tears and the strong suggestion that it is present at relatively increased levels in cases of ragweed and vernal conjunctivitis is a matter of potential importance. Increased levels of IgE in the serum of allergic asthmatic,[12] ragweed sensitive,[13] and eczematous patients,[14] combined with the finding of cells producing IgE near mucous membranes[6] suggest that this immunoglobulin is the mediator of atopic hypersensitivity at the surface of eye.

Immunochemical investigations have indicated the possibility that two IgE antibody molecules on the target-cell surface are bridged together by a single antigen molecule to initiate the production of inflammation.[2] Indeed, extremely small amounts of soluble IgE antibody-ragweed antigen complexes formed in vitro are maximally active at a two: one ratio ($Ab_2$ Ag) directly causing the wheal and erythema reaction on intracutaneous injection in normal subjects.[2] This information, combined with the findings of relatively increased IgE in the tears of patients with vernal conjunctivitis and ragweed conjunctivitis, suggests that such antigen-antibody complexes fixed to target cells near the conjunctival mucous membrane could produce inflammation and result in clinical disease.

Over 40 years have elapsed between the demonstration of the Pausnitz- Küstner reaction and the recent understanding that IgE is the mediating antibody present in serum in amounts previously too small to detect. As better methods of quantitatively measuring total IgE are improved over the present laborious procedures, elevated IgE may be found in a variety of diseases in which elevated immunoglobulin has not been detected.

With the increased understanding of IgE that will result from the quantitative determination of this immunoglobulin in tears and sera of normal individuals and patients with eye disease, IgE determination may become of value to the clinician faced with the problem of defining the presence of a hypersensitivity component in patients whose inflammation of the external eye may be of infectious, allergic, toxic, or combined etiology.

## Summary

IgE was demonstrated by a specific radioimmunodiffusion procedure and was found in detectable amounts in all tear samples studied and in increased amounts in seven out of nine patients suffering from presumed allergic disorders of the external eye, including all five cases of vernal conjunctivitis.

IgE may represent a local immune system at the mucous membrane surfaces of the eye mediating allergic phenomena in man and causally related to certain allergic disorders.

A further definition of the IgE system in man may be of clinical importance. IgE levels in tears might someday serve as a test for the presence of an atopic component in inflammatory states and in the diagnosis of inflammations of the cornea and conjunctiva.

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# CLASSIFICATION OF THE CHOROIDAL ATROPHIES

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A number of diseases of the ocular fundus are characterized by abnormalities of the choroidal vasculature. These conditions vary in severity with changes ranging from atrophy of the choriocapillaris only in the posterior eyegrounds to an almost complete absence of all choroidal vascular elements throughout most of the eyegrounds.

Heretofore, most descriptions of these clinical entities have been based on direct ophthalmoscopic observations, and as a result, the literature abounds with vague, erroneous, and misleading terms. The recent introduction of electrophysiologic methods of analysis and angiographic techniques, coupled with accumulated histologic data, have given fresh insight into the nature of many of these conditions.

It is the purpose of this paper to describe and classify those choroidal atrophies believed to be primary in nature, progressive, and not associated with obvious toxic or inflammatory factors.

## METHODS

Thirty patients with choroidal atrophy were selected for study. These patients could be conveniently grouped according to the position of the lesion and the extent of the involvement of the fundus, and by the degree of involvement of the different layers of the choroidal vasculature.

*Group 1—Regional choroidal atrophies*—This group included patients in whom the involved area was limited to the posterior pole of the eye. This group was subdivided into (a) patients with choriocapillaris atrophy alone, and (b) patients with total choroidal vascular atrophy.

*Group 2—Diffuse choroidal atrophies*—This group consisted of patients with extensive involvement of the eyegrounds, and it was subdivided into (a) patients with choriocapillaris atrophy alone, and (b) patients with total choroidal vascular atrophy. The latter subgroup (b) was further divided on the basis of inheritance into (1) patients with autosomal inheritance, and (2) patients with X-linked inheritance.

All patients received routine ophthalmoscopic evaluation, visual field studies with the Goldmann perimeter, color vision testing, dark adaptation, electroretinogram (ERG), and frequently, electro-oculogram (EOG) studies. The techniques used for these tests have been described.[1-3]

A modified Zeiss fundus camera was used for fluorescein angiography. This permitted rapid sequence photography and automatic recording of the time of photography. The apparatus and technique are described elsewhere.[4]

## CLASSIFICATIONS

### REGIONAL CHOROIDAL ATROPHIES

#### CHORIOCAPILLARIS ATROPHY INVOLVING THE POSTERIOR EYEGROUNDS

There are three topographical patterns that the disease may follow: (1) involvement of the macula alone, (2) involvement of the peripapillary area, and (3) involvement of the paramacular area.

1. Involvement of the macula alone. Disease at this site was previously called central choroidal sclerosis, central choroidal vascular atrophy, central areolar choroidal sclerosis, central progressive areolar choroidal dystrophy, and central choroidal angiosclerosis.[5-8]

2. Involvement of the peripapillary area. Disease involving this area was previously

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termed peripapillary choroidal sclerosis. This form may be associated with angioid streaks, and on occasion may precede them. Occasionally, this type is characterized by finger-like extensions of choriocapillaris atrophy from the primary area of involvement around the disk.

3. Involvement of the paramacular area. This is also referred to as circinate choroidal sclerosis.[9] This form may expand to occupy most of the posterior eyegrounds.

*Clinical features*—The age of onset is thought to range from about 20 to 40 years. Vision may not be significantly affected unless the macula is involved. In familial cases, the inheritance has been either autosomal recessive or dominant.[5-11]

In our patients the earliest fundus change was atrophy of the retinal pigment epithelium. This was characterized by pigment stippling and mottling, with occasional formation of clumps. These areas demonstrated hyperfluorescence on fluorescein angiography, typical of a pigment epithelial abnormality.[12] According to Sorsby and Crick,[6] the earliest changes are nonspecific edematous-exudative reactions in the macular and perimacular areas, or an atrophic reaction—pigment mottling with exudative reaction around it. We have not seen such changes in what we thought were early cases, or at the borders of lesions which later showed progression.

Choriocapillaris atrophy probably closely follows initial changes in the pigment epithelium. As a result of both choriocapillaris atrophy and pigment epithelium disease, the larger choroidal vessels become visible, and are seen as tortuous, yellow-white cords, often with white deposits along their borders. These vessels are vividly outlined through all stages of fluorescein angiography.*

As the disease progresses, the area of choriocapillaris atrophy slowly expands centrifugally, revealing the underlying intermediate-sized and larger choroidal vessels.

The appearance and evolution of the disease is usually symmetrical; however, occasionally one eye may show advanced disease with the fellow eye only minimally involved.

The retinal vasculature may be attenuated in some cases, with the optic disk assuming the waxy appearance typical of retinitis pigmentosa.

*Retinal function*—Visual acuity and color vision are moderately to severely abnormal (except in cases where the fovea has been spared). Peripheral visual fields are normal. Central and paracentral scotomas reflect macular involvement by the disease process.

Subjective dark-adaptation studies, which measure retinal function away from the area of obvious ophthalmoscopic involvement, are frequently mildly to moderately abnormal. The ERG and EOG, which reflect functional integrity of large retinal areas, are also frequently abnormal. Thus, from a functional standpoint, the abnormality is more widespread than would be expected from ophthalmoscopic examination.

*Histology*—Histologic studies of involved areas have shown atrophy of the choriocapillaris, pigment epithelium, and neuroepithelium.[13-15] Bruch's membrane was relatively normal in two of these eyes studied,[13,14] but definitely abnormal in the third.[15]

## Case reports

Case 1 illustrates the following points: (1) progression of eyeground changes, (2) asymmetry, and (3) impairment of peripheral retinal function.

*Case* 1—This 64-year-old man has a sharply defined area of choriocapillaris atrophy in the macula (Fig. 1). He gave a history of experiencing some visual loss in his left eye 10 years earlier. He also reported that his maternal grandmother had grossly impaired eyesight when she was middle-aged but the cause of her blindness is uncertain. An autosomal dominant inheritance, with lack of penetrance of the gene in the patient's mother, is possible, but unsubstantiated.

*Progression of eyeground changes*—A slight in-

* Normally, the larger choroidal vessels are not seen beyond the early or midretinal venous phase of angiography because of the dense homogeneous background formed by the normal choriocapillaris which is completely filled by this stage.[4]

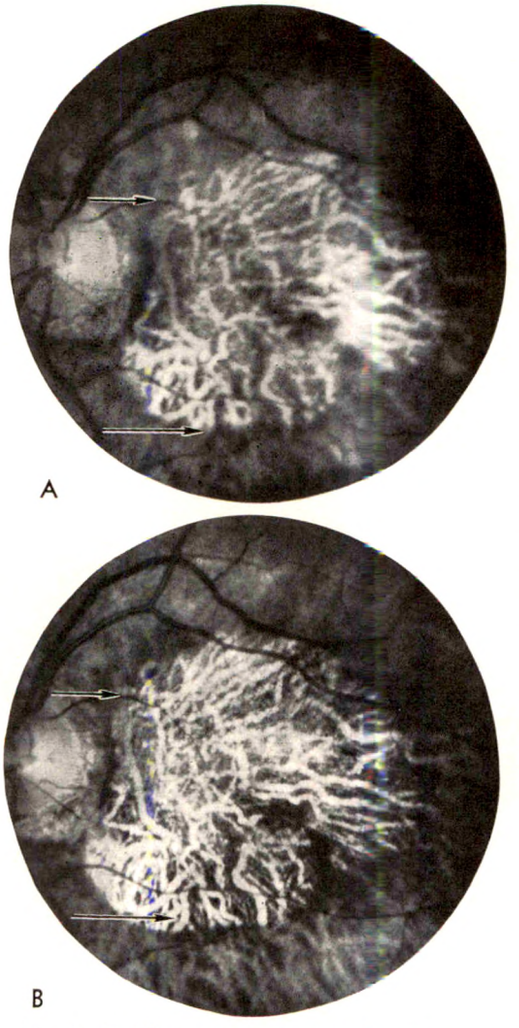



Fig. 1. (Krill and Archer). Case 1. Left posterior eyegrounds of a 64-year-old man with choriocapillaris atrophy at the macula. (A) Increased visibility of the larger choroidal vessels is seen in July, 1967. These vessels are tortuous, and of variable color and caliber. The area of pigment epithelial and choriocapillaris atrophy has a sharply defined border. Fine pigment clumps are scattered throughout the area of involvement. (B) In August, 1969, there is an expansion of the involved area (compare arrows in A and B), and there is better definition of the large and intermediate-sized choroidal vessels.

crease in the total area of choriocapillaris atrophy occurred from July of 1967 to August of 1969 (compare arrow sites in Figs. 1-A and B). The larger choroidal vessels have not altered during this time, although some appear to be more sharply defined. The small branches of the larger choroidal vessels are more obvious.

*Asymmetry*—The fovea is minimally affected in the right eye, but is directly involved in the left. Right vision has remained 20/25, whereas left vision has deteriorated to 20/300.

*Peripheral retinal function impairment*—Peripheral visual fields are normal. Dark adaptation beyond the posterior eyegrounds is normal. A subnormal ERG (Fig. 2) and an abnormal EOG (Fig. 3) were obtained from both eyes.

Cases 2 and 3 illustrate the following points: (1) progression of eyeground changes, (2) sparing of the fovea, and (3) impairment of peripheral retinal function.

*Case 2*—This 58-year-old man has choriocapillaris atrophy throughout most of the posterior eyegrounds (Fig. 4). Visual symptoms began about the age of 35 years. A 65-year-old sister with the same condition had severe visual impairment (Fig. 5). Autosomal recessive inheritance is presumed.

*Progression of eyeground changes*—A considerable extension of the total area of choriocapillaris atrophy occurred from 1963 to 1969 (compare arrow site in Fig. 6-A with that in 6-B). No edema or exudates were seen at sites of progression. Pigment stippling, depigmentation, and increased visibility of the underlying larger choroidal vessels were the earliest changes in such areas.

There was no significant atrophy of the large choroidal vessels during the six-year follow-up period. However, the large choroidal vessels became more easily visualized (compare Figs. 6-A and B), and a lacy intertwining network of fine branches from these vessels was eventually seen. In both 1963 and 1969 the retinal arterioles were slightly attenuated and the optic disk showed a waxy pallor.

*Sparing of fovea*—Visual acuity in 1963 and 1969 was 20/25 in the right and 20/40 in the left eye. The patient's sister, with the same disease, has been severely blind for many years, indicating that the site of this disease may vary among affected members of the same family.

*Peripheral retinal function*—Peripheral visual fields were normal, but large paracentral scotomas, corresponding to the areas of ophthalmoscopic involvement, were evident in Case 2. Dark adaptation, mildly abnormal in 1963, was markedly abnormal in 1969. (The final threshold was one-half log unit above the normal mean plus two standard deviations in 1963, but in 1969 was 2.5 log units above this value.) The ERG, subnormal in 1963, was considerably smaller on retesting in 1969 (Fig. 7).

Case 3 illustrates parapapillary choriocapillaris atrophy.

*Case 3*—This 45-year-old man had normal vision and choriocapillaris atrophy around the disk (Fig. 8). There were four finger-like extensions of the area of involvement. There were a few angioid streaks in the upper temporal atrophic area. Visual

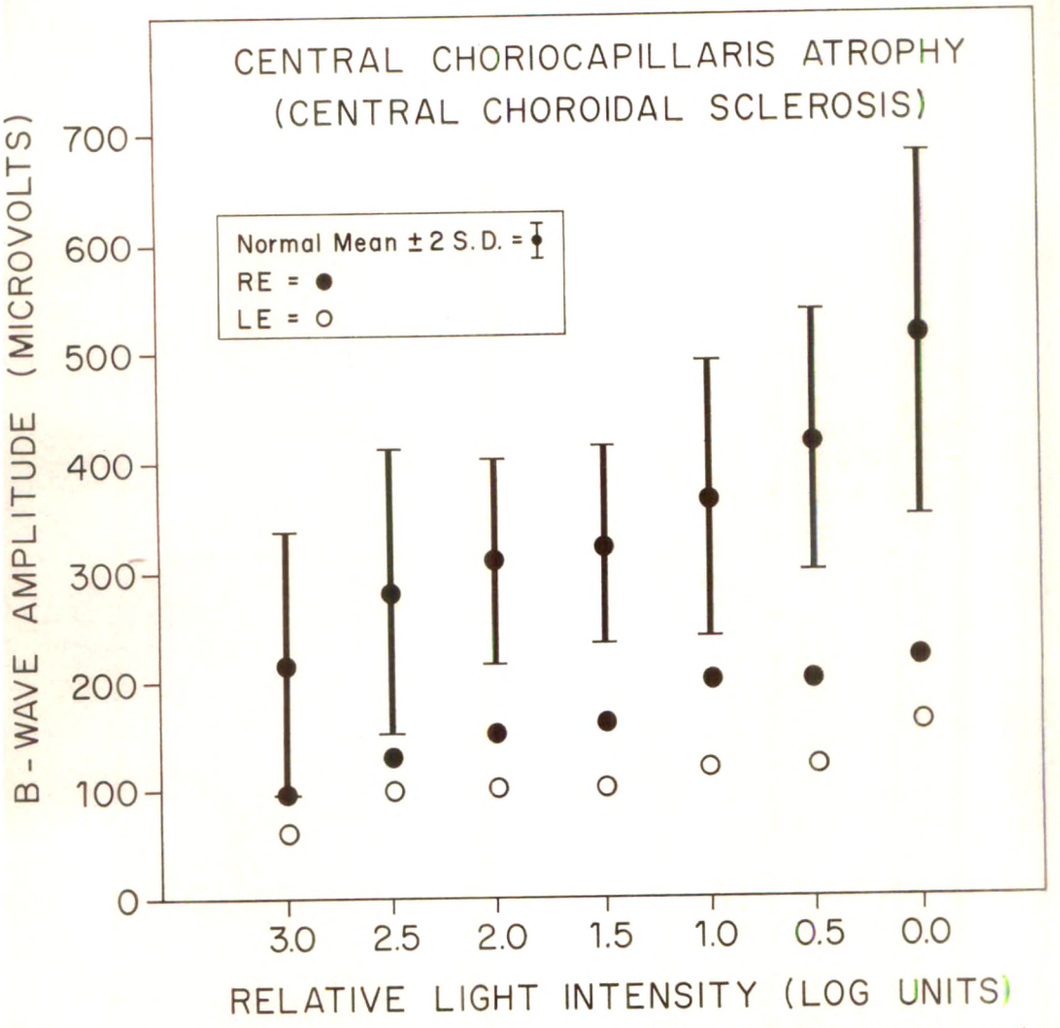



Fig. 2 (Krill and Archer). B-wave amplitudes from a normal control population (normal mean plus or minus two standard deviations) and from Case 1. Note that b-wave amplitudes are subnormal at all intensities of stimulation used.

fields demonstrated enlarged blind spots; all other visual function tests were normal.

TOTAL CHOROIDAL VASCULAR ATROPHY INVOLVING THE POSTERIOR EYEGROUNDS

This condition is characterized by atrophy of the large choroidal vessels, as well as the choriocapillaris. The atrophy often has a serpiginous-like configuration. There are four sites of involvement: (1) the macula alone, (2) the posterior eyegrounds, (3) nasal and temporal foci, and (4) the disk.

When confined to the macula or throughout most of the posterior eyegrounds, the disease has been called choroidal vascular abiotrophy helicoid, serpiginous degeneration of the choroid,[16] or central gyrate atrophy.[8]

When the foci is nasal or temporal, the disease has been termed progressive bifocal chorioretinal atrophy.[17] It begins as a discrete temporal focus of semilunar configurations and feathery edges. A similar nasal focus develops later in life.

When the site is the disk, names include

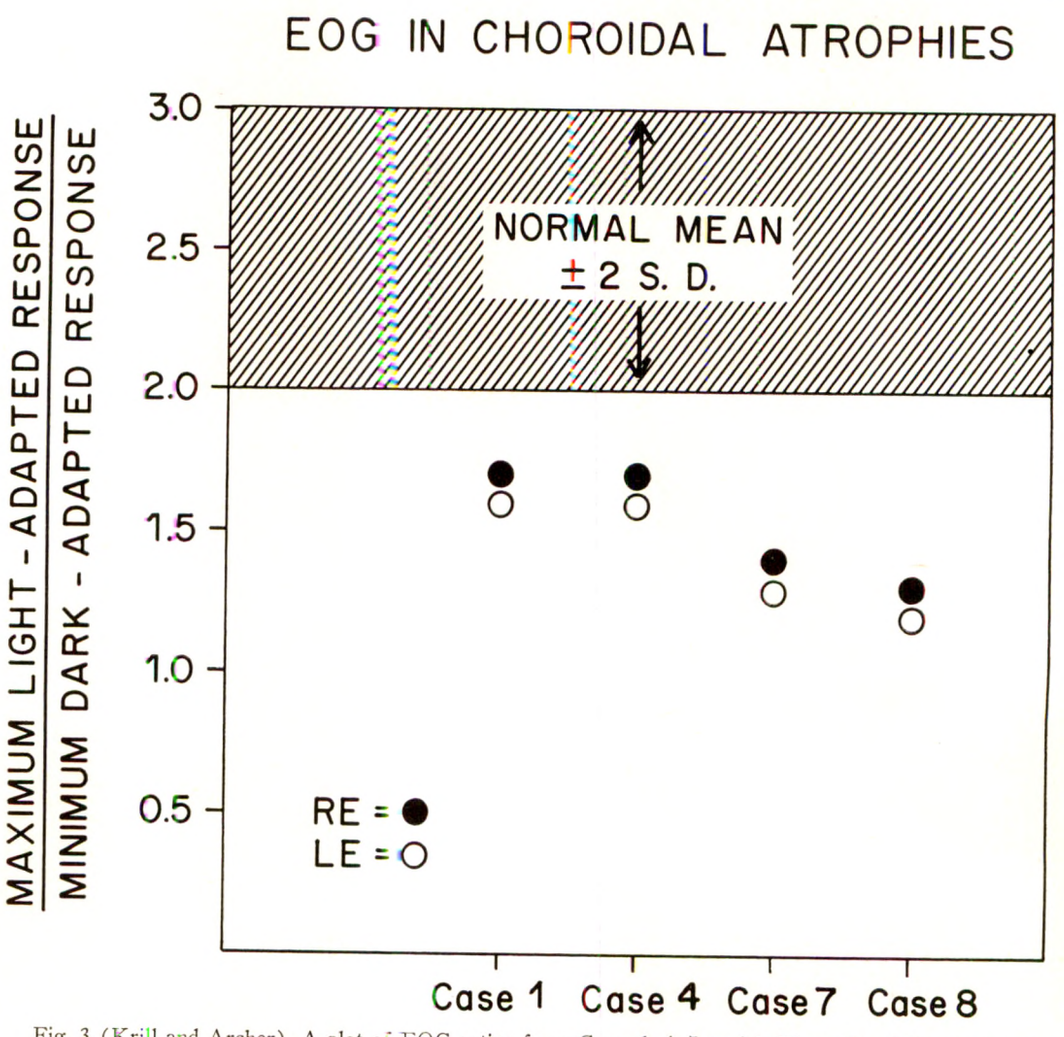



Fig. 3 (Krill and Archer). A plot of EOG ratios from Cases 1, 4, 7, and 8. The ratio of the maximum light adapted response to the minimum dark adapted response for each patient is plotted and compared with a standard control group (normal mean plus or minus two standard deviations). These patients all had abnormal values.

helicoid peripapillary chorioretinal atrophy,[18,19] choroiditis areata,[20] circumpapillary dysgenesis of the pigment epithelium,[21] and chorioretinitis striata.[22] In such cases, wing-like radial extensions are characteristic.

*Clinical features*—There is no uniform age of onset for the conditions discussed here. Progressive bifocal chorioretinal atrophy may begin in infancy. Total choroidal vascular atrophy around the disk has been observed to develop between the ages of four to 43 years, with the majority of cases developing in the first 25 years of life.[7] The serpiginous form of atrophy involving the macula or posterior eyegrounds probably begins somewhere between the ages of 35 to 55 years.

The inheritance is clearly autosomal dominant in progressive bifocal chorioretinal atrophy.[17] Involvement of both a mother and son with a peripapillary atrophy suggests that this type of inheritance may be operant in some of these patients.[7,23] However, almost all the other cases are sporadic, sug-

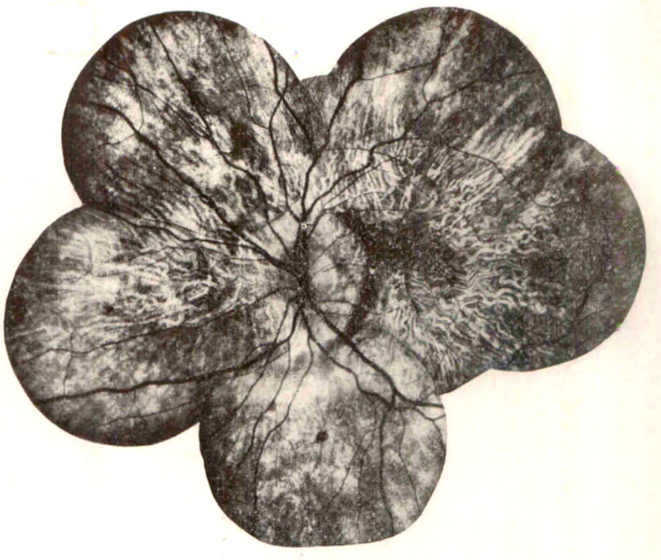


Fig. 4 (Krill and Archer). Case 2. Composite photograph of the left posterior eyegrounds. The choriocapillaris atrophy involves much of the posterior eyegrounds.

gesting either an environmental origin or autosomal recessive inheritance for cases which are genetic in origin.

The earliest change consists of a homogeneous gray, edema-like appearance of the involved retina, probably representing a change in the pigment epithelium. This type of lesion is frequently surrounded by a zone of pigment stippling and atrophy indicative of further deterioration of the pigment epithelium. These areas show hyperfluorescence on fluorescein angiography typical of abnormal pigment epithelium.[24] This early lesion advances to a stage of total choroidal vascular atrophy in which there are only a few large choroidal vascular remnants. There does not appear to be an intermediate stage during which only the choriocapillaris atrophies.

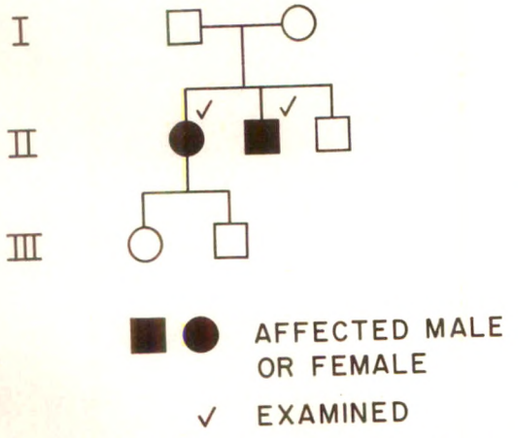



Fig. 5 (Krill and Archer). Pedigree of Case 2.

*Retinal function*—The unusual geographic configuration often causes asymmetrical impairment of central visual acuity. Although the atrophy appears limited to the posterior eyegrounds, retinal function tests (dark adaptation, ERG, EOG) usually show abnormal response beyond the obviously involved area. Visual fields are usually normal except for central and paracentral scotomas corresponding to obviously involved areas.

## Case reports

Case 4 illustrates the following points: (1) early eyeground changes, (2) progression of eyeground changes, and (3) central and peripheral visual function impairment.

*Case* 4—This 65-year-old man had serpiginous-like areas of total choroidal vascular atrophy at both maculas (Fig. 9). He complained that his vision had been "failing" in both eyes for at least six months. There was no family history.

*Early eyeground changes*—A homogeneous grayish area was evident at the superior portions of the lesions in 1963 (see A in Fig. 9-A and B).

*Progression in eyeground changes*—Considerable progression occurred between 1963 and 1969 (compare Fig. 9-A and B with Fig. 9-C and D). Almost

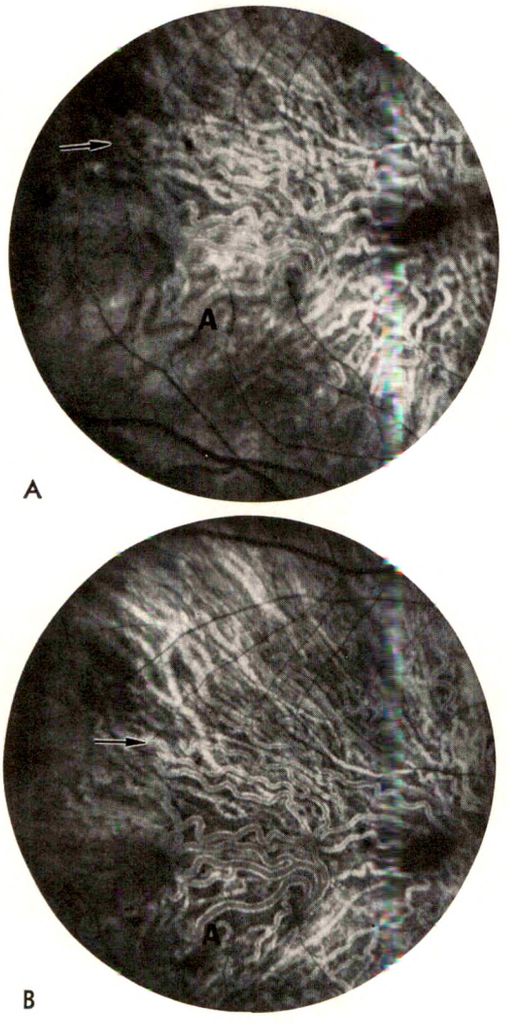



Fig. 6 (Krill and Archer). Case 2, posterior eyegrounds. (A) The right macula in 1963 and (B) the right macula in 1969. During the period of time between 1963-69, no atrophy of the larger choroidal vessels occurred; however, these vessels are more obvious in the recent photographs (compare sites marked A). There has been an expansion of the area of pigment epithelium and choroidal atrophy (compare arrow sites).

the entire macular area of both eyes was involved in 1969. In addition, the atrophy extended inferior to the optic disk and temporal to the macula (Fig. 9-C and D). The temporal retinal arterioles had become slightly attenuated by 1969.

*Central and peripheral visual function impairment*—Visual acuity was 20/30 in both eyes in 1963, but had deteriorated to 20/200 in both eyes by 1969. Complete retinal function studies were done only in 1969. Visual fields were normal apart from large central scotomas. Dark adaptation was normal beyond the involved areas. An EOG was abnormal (Fig. 3) and the ERG subnormal (Fig. 10).

Case 5 illustrates the following points: (1) early eyeground changes, (2) progression of eyeground changes, and (3) asymmetry, with (4) normal peripheral visual function.

*Case* 5—A 52-year-old man with a five-year history of left visual loss shows atrophy of the choroidal vasculature throughout most of the posterior eyegrounds (Fig. 11). The right eye had slight visual loss of recent onset. There was no family history of similar ocular disease.

*Early eyeground changes*—The temporal portion of the left macula showed a homogeneous grayish edema-like opacification (letter A in Fig. 12-A). There appeared to be no intraretinal edema at this site on slit lamp examination. Nasal to this area there is pigment epithelial atrophy with pigment stippling (Fig. 12-A). A fluorescein angiogram showed hypofluorescence in the area of gray opacification (see arrow in Fig. 12-B) and a spotty hyperfluorescence in the adjacent depigmented region.

*Progression of eyeground changes*—Both eyes showed marked progression of choroidal atrophy. Note changes in the right eye over a one-year period (compare arrow sites in Figs. 12-C in 1968 and 12-D in 1969).

*Asymmetry*—On initial examination in 1966, right vision was 20/25 and left vision was 20/200. On last evaluation in 1969, right vision was still 20/25, but 10/200 in the left eye.

*Peripheral visual function*—There was a large left central scotoma and bilateral irregular paracentral scotomas coincident with the areas of ophthalmoscopic abnormalities. Peripheral fields were normal; an ERG in 1969 revealed responses at the lower limit of normal (Fig. 10).

## Malignant myopia

We consider cases of malignant myopia to belong to the group of regional choroidal atrophies, and as most of these cases eventually show atrophy of both large and small choroidal vessels, they fit into the subgroup of total choroidal vascular atrophies.

These patients usually have at least six diopters of myopia. Discrete areas of atrophy, eventually involving small and large choroidal vessels, the retinal pigment epithelium, and possibly a portion of the external retina, are seen in the posterior eyegrounds of such patients.[25]

Focal areas of atrophic choriocapillaris and pigment epithelium are seen initially. They often have pigment clumps around

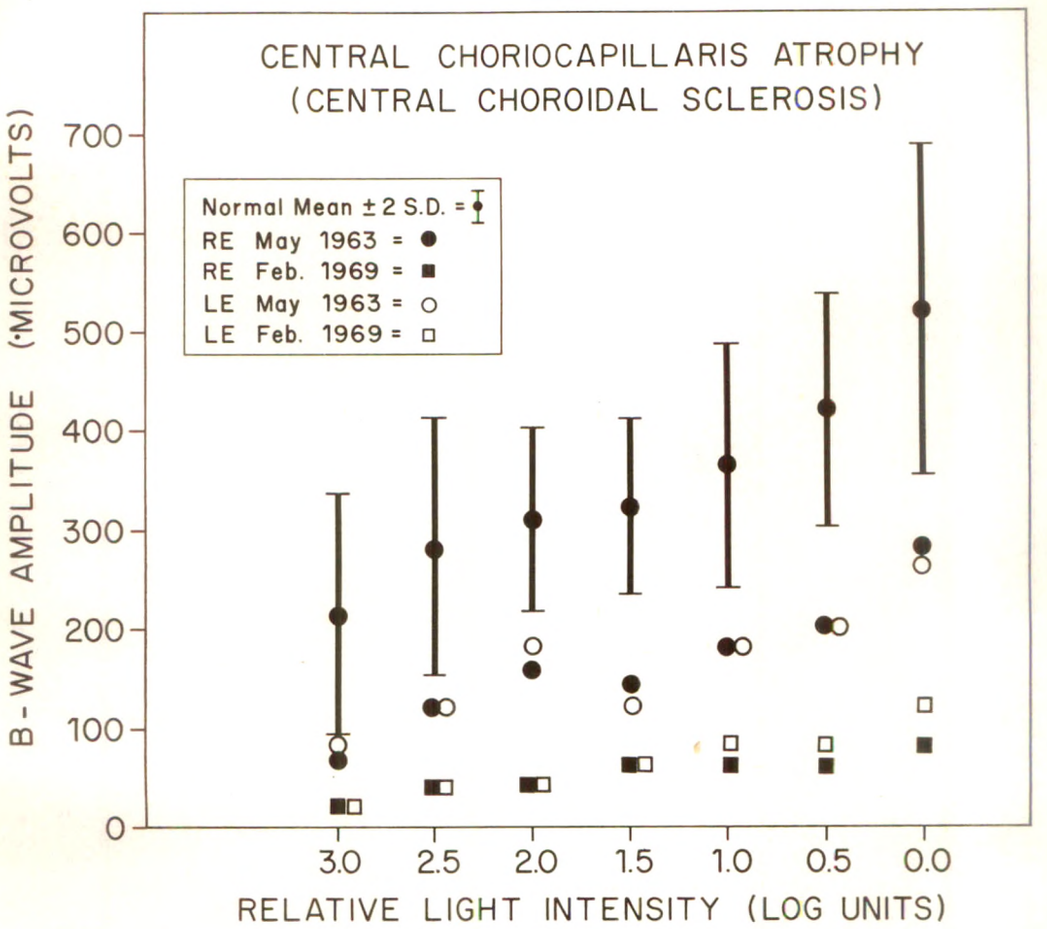



Fig. 7 (Krill and Archer). Case 3. B-wave amplitudes plotted from both eyes in 1963 and from both eyes in 1969 at seven different intensities of light stimulation. The data from this patient are compared with a normal control group. Note that subnormal b-wave amplitudes were obtained on initial evaluation and that a marked decrease in these amplitudes occurred over the six-year period.

their borders. These focal areas may coalesce and form large geographic areas of choroidal vascular atrophy, often merging with an enlarged peripapillary degenerative area.

Changes at the optic disk are common. A border of chorioretinal atrophy and pigmentation may appear on the temporal side of the disk (temporal or myopic crescent), or it may surround the entire disk. Commonly, an oblique entry of the optic nerve into the eyeball may cause an extension of the retina over the nasal portion of the optic disk (supertraction crescent or supertraction of the retina).

A posterior ectasia or staphyloma, usually nasal to the optic disk, is common in eyes with very high myopia (e.g., over 12 diopters). The ectatic area appears as an abrupt out-pouching in which the fundus is pale and the choroidal pattern more prominent than in the surrounding eyegrounds.

Fine ruptures in Bruch's membrane may be seen as an irregular network of glistening linear yellow-white streaks known as laquer marks or cracks. Hemorrhages, probably originating from the choriocapillaris, can occur in such areas. These deep macular hemorrhages may leave a fibrotic scar or a pig-



Fig. 8 (Krill and Archer). Case 3. A 45-year-old man with normal vision and early angioid streaks. Note area of choriocapillaris atrophy around the disk with finger-like extensions in each quadrant.

mented fleck called a Fuchs spot.

Peripheral chorioretinal atrophic changes are a common counterpart to the posterior disease. Scattered, sharply delineated atrophic foci involving all choroidal vascular elements and a portion of the retina appear throughout the entire periphery. These are referred to as pavingstone or cobblestone degeneration.[26] Numerous small cystoid spaces often develop between the equator and ora serrata.

Vision is significantly impaired in malignant myopia, and large central scotomas are noted on visual fields. Peripheral visual fields are usually normal, because peripheral changes are usually beyond the visual field limits. Both the ERG and EOG are usually subnormal. Dark adaptation beyond the macular area is normal or slightly elevated.

Familial cases have been reported with either autosomal dominant or recessive inheritance, although the latter is more common.[27]

### Case report

*Case* 6—This 45-year-old woman had 20/200 vision in both eyes and choroidal vascular atrophy throughout the posterior eyegrounds. Several large discrete areas of almost total choroidal vascular atrophy were present around and near the optic disk (Fig. 13). Superior to the optic disk, there was only a partial atrophy of the larger choroidal vessels. Pavingstone degeneration and pseudocysts were widespread in the peripheral eyegrounds. Central scotomas were noted on visual fields and a subnormal ERG was obtained.

### Diffuse choroidal atrophies

The diffuse choroidal atrophies closely mimic the regional choroidal atrophies in the type of changes occurring in the choroidal vasculature. However, the diffuse choroidal atrophies are distinguished by the widespread nature of the disease process and greater disturbance of peripheral retinal function. The macula may be spared or only mildly involved until the later stages of the disease.

### Diffuse choriocapillaris atrophy

This condition has been referred to as generalized choroidal angiosclerosis, diffuse choroidal sclerosis, or generalized choroidal sclerosis.[7,8,28]

*Clinical features*—Typically, the choriocapillaris atrophy extends out to the equatorial region or beyond. There may be variability among affected members of a family.[8] Some members may show choriocapillaris atrophy only in the posterior eyegrounds, even at an advanced age.

The hereditary transmission is usually autosomal dominant, although several cases have occurred sporadically, suggesting an autosomal recessive inheritance. Sex-linked forms will be discussed later in this paper.

Choriocapillaris atrophy usually becomes clinically apparent in the third or fourth decade of life, although it has been occasionally observed in the first or second decade. It usually progresses slowly as age advances.

In our experience, the disease usually begins with retinal pigment epithelial atrophy accompanied by pigment stippling and mottling. There is increased visibility of the larger choroidal vessels in these areas which hyperfluoresce on fluorescein angiography. Typically, the process originates in the macula or peripapillary areas and slowly spreads

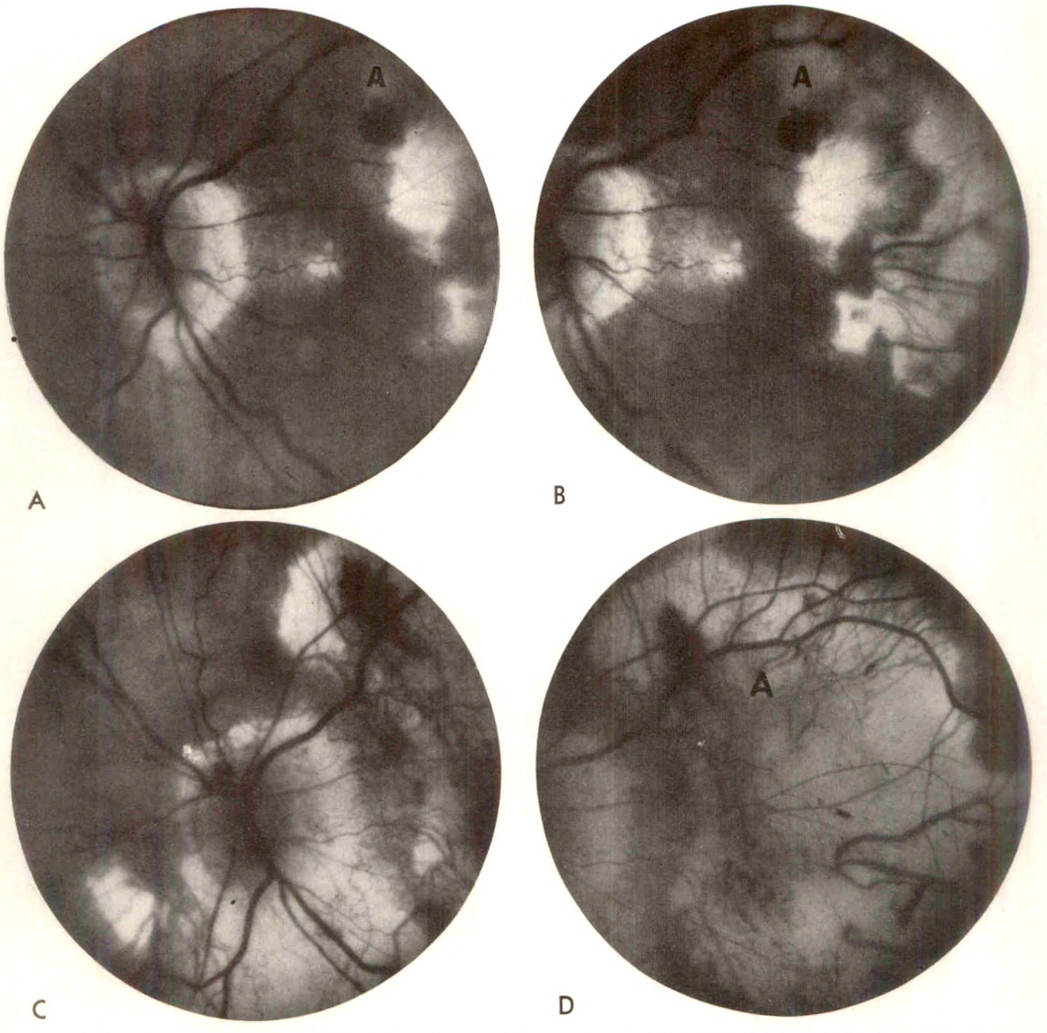



Fig. 9 (Krill and Archer). Case 4. Serpiginous-like areas of total choroidal vascular atrophy involving the left macula and peripapillary region. Figs. A and B were taken in 1963 and Figs. C and D in 1969. The geographic configuration is characteristic. Homogeneous gray areas were evident at the superior portions of the serpiginous lesion (letter A in Figs. A and B). This area is typical of the earliest change noted in this condition. There has been considerable extension of the atrophic process over the six-year period. Compare the site marked A in Fig. D, taken in 1969, with the same site in Figs. A and B, taken in 1963. In most areas there is a considerable absence of the larger choroidal vessels. The dark area seen in the superior portion of each photograph represents a pigment clump.

towards the periphery. In advanced disease, the retinal vessels become attenuated and the optic disk takes on a waxy appearance. Central visual loss may occur early in this condition, although the foveal area may be spared until relatively late in the disease. Night blindness is a characteristic early complaint.

*Retinal function*—Peripheral visual fields are abnormal. Dark adaptation studies and the EOG are markedly abnormal. The ERG is frequently abnormal and extinguished.

*Histology*—One eye, with what appears to be a diffuse choroidal atrophy, has been examined histologically.[29] There was an absence of much of the choriocapillaris, pigment epithelium, photoreceptors, and Bruch's mem-

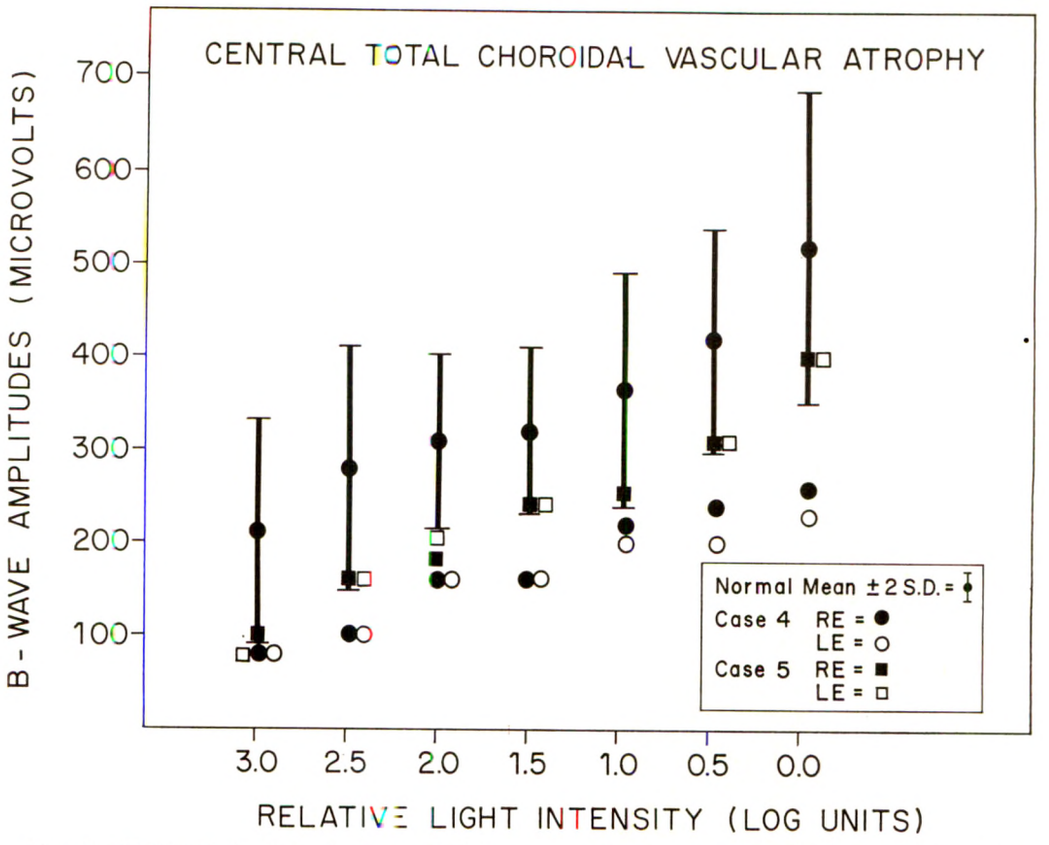



Fig. 10 (Krill and Archer). Cases 4 and 5. B-wave amplitudes at seven different intensities. These amplitudes are subnormal in Case 4 and at the lower limit of normal in Case 5, in spite of ophthalmoscopic changes only in the posterior eyegrounds.

brane extending out toward the equator. The most severe atrophy was noted in the posterior eyegrounds.

### Case reports

Case 7 illustrates the following points (1) early eyeground changes, (2) functional impairment and progression.

*Case 7*—This 36-year-old woman demonstrates an early form of the disease (Fig. 14). She noted central visual impairment at the age of 28 years. She had no other visual complaints. Other affected members of the family include a sister (Case 8), a 46-year-old brother with abnormal vision and severe night blindness, and two great aunts (maternal) with histories of blindness at middle age (Fig. 15). The inheritance is probably autosomal dominant with variable penetrance of the gene (accounting for the lack of disease in the mother).

*Early eyeground changes*—Fine and coarse pigment stippling, with increased visibility of the underlying choroidal pattern, is evident up to the equator. In the macula (Fig. 14-A) the disease was more advanced, and several sharply defined areas of choriocapillaris atrophy were noted. On fluorescein angiography, a diffuse hyperfluorescence reflected the widespread disturbance of pigment epithelium (Fig. 14-B). There was visibility of the underlying choroidal vessels in the macula throughout fluorescein angiography (arrow in Fig. 14-B).

*Functional impairment and progression*—Vision was 20/50 in the right and 20/40 in the left eye in 1957. In 1965, vision was 20/200 in both eyes. In 1969, peripheral visual fields, last studied in 1969, were normal except for large central scotomas. Dark adaptation studies, done in 1969, were slightly abnormal (one log unit above the normal mean plus two standard deviations). An ERG was normal in 1965, but was subnormal in 1969 (Fig. 16).

Case 8, the sister of the preceding patient (Case 7), illustrates the following points: (1) advanced eyeground changes, (2) pro-

gression of eyeground changes, and (3) progressive changes in visual function.

*Case* 8—This 56-year-old woman demonstrated an advanced form of the disease (Fig. 17). She had a 20-year history of poor visual acuity and night blindness.

*Advanced eyeground changes*—The larger choroidal vessels are visible throughout the fundus (Figs. 17-A and B). Most of these vessels appear narrowed, with white deposits along their walls. Some were evident as yellow-white cords. The larger choroidal vessels were visible throughout fluorescein angiography[12] (Fig. 17-C). (They normally are seen only during the early and mid-retinal venous phases.[1]) Many vessels which appeared to be "sclerosed" on ophthalmoscopic evaluation were patent to dye. There was a prolonged choroidal circulation time.

*Progression of eyeground changes*—Subtle changes occurred in areas of involvement. Some of the larger and intermediate-sized choroidal vessels became more sharply defined.

*Progressive changes in visual function*—Visual acuity was 20/200 in each eye in 1965 and 10/200 in 1969. Visual fields revealed bilateral ring and central scotomata in 1965. By 1969, peripheral fields had become constricted. Dark adaptation showed further deterioration (about 3.5 log units above the normal means plus 2 standard deviations in 1969 compared to about 2.5 log units above this value in 1965). In 1965, subnormal responses on the ERG were noted and in 1969, a practically extinguished record was obtained (Fig. 16).

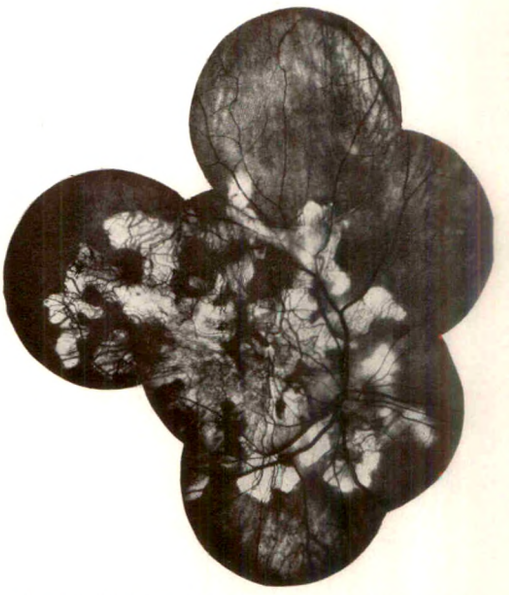


Fig. 11 (Krill and Archer). Case 5. Right fundus of a 50-year-old man with total choroidal vascular atrophy confined to the posterior eyegrounds. Note geographic configuration of the atrophic areas, with intervening normal retina and choroid. Pigment clumps are scattered at random in the involved areas.

### Diffuse total choroidal vascular atrophy

*Autosomal inheritance*—This condition has been called gyrate atrophy of the choroid and retina.[7,8,30] The inheritance is usually autosomal recessive and the disease typically starts in the mid-peripheral eyegrounds and extends centrally and peripherally. In the autosomal dominant form, there may be great variability in the degree of involvement.

*Clinical features*—The disease is usually first noted between the ages of 20 and 30 years. The youngest patient described was six years of age. The initial changes consist of sharply defined areas of choroidal atrophy in the equatorial fundus. Such areas have serrated or scalloped margins and appear in patches throughout the fundus. In time, the atrophic areas become confluent and expand centrally and peripherally. The fundus eventually assumes a yellow-white color (from the background sclera) with scattered pigment and choroidal vascular remnants. The macula generally remains intact until late in the disease. The retinal vessels may become attenuated, and in advanced cases optic atrophy may occur. Myopia and complicated cataracts frequently develop in association with the disease.

Night blindness is usually the earliest complaint. Visual field abnormalities correspond to ophthalmoscopic changes. A ring scotoma may be the initial visual field abnormality. Vision may be normal even in fairly advanced cases, since the macula is often spared until late in the disease. The ERG and EOG are usually abnormal, even in the early stages; in advanced disease, both tests are severely abnormal, indeed to the degree seen in retinitis pigmentosa.

### Case reports

The following three cases demonstrate these points: (1) typical eyeground changes,

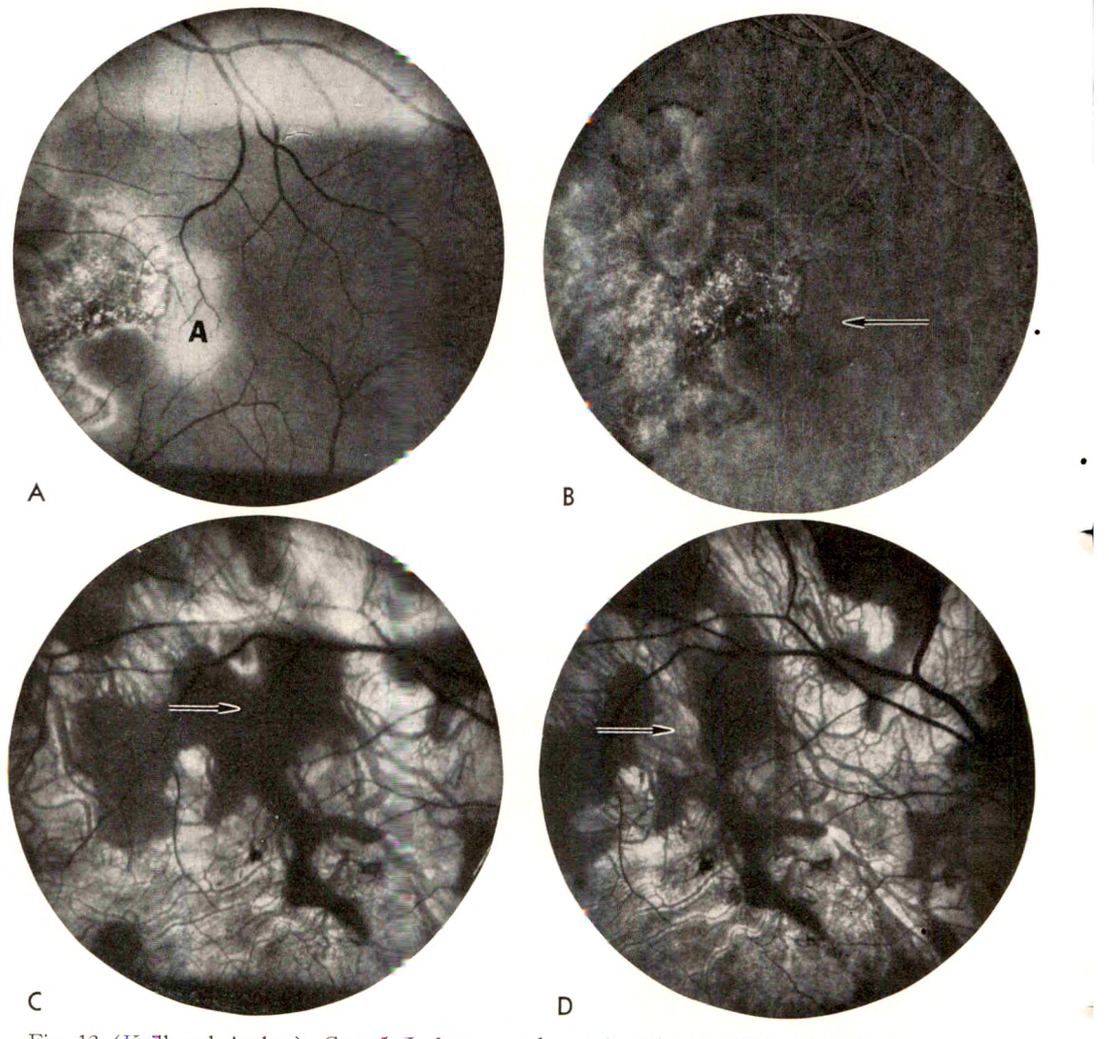



Fig. 12 (Krill and Archer). Case 5. Left temporal macula, taken in 1966. (A) Homogeneous gray opacification was seen at the advancing edge of a lesion (letter A is in the center of this area). At the nasal aspect of this area pigment epithelial atrophy and stippling are evident. The superior opacification is an artefact. (B) Fluorescein angiogram taken during the late retinal venous phase of the same area in Figure A. The site of gray opacification is hypofluorescent (see arrow). Fig. C (1968) and Fig. D (1969) demonstrate extension of areas of total choroidal vascular atrophy (compare arrows which point to the same site).

(2) late involvement of the fovea, and (3) severe impairment of peripheral retinal function.

*Cases* 9-11—These three siblings (Fig. 18) had various degrees of diffuse total choroidal vascular atrophy. The sister (Case 9) was 45 years of age and the two brothers were 46 (Case 10) and 50 (Case 11) years of age. All complained of night blindness for at least 20 to 25 years, and more recently, loss of peripheral vision. The sister had had abnormal central vision in both eyes for two years. The younger brother had had poor left central vision for four or five years. The mother had severe night blindness from an early age (Fig. 18). Therefore, it is likely that the inheritance of the choroidal atrophy in this family is autosomal dominant.

*Typical eyeground changes with variable involvement.*—All showed large areas of almost total chorcidal vascular atrophy throughout their posterior eyegrounds and to some extent in the periphery (Figs. 19 and 20). In Case 11, disease was confined mainly to the posterior eyeground area (Fig. 20-C).

Case 10 had changes almost up to the equatorial region (Figs. 20-A and B), and in Case 9 the disease extended beyond the equatorial region (Figs. 19-A and B). There were sharp zones of transition between normal and involved areas of the fundus. The border areas often had a scalloped appearance with evidence of abnormal pigment epithelium adjacent to the areas of choroidal atrophy. There were no such sharp transitional areas in the two patients with only choriocapillaris atrophy (Cases 7 and 8).

*Late involvement of the fovea.*—Despite a 20-year history of night blindness, Case 11 had vision of 20/20 in both eyes. Case 10 had 20/20 vision in the right eye and 20/80 in the left eye. Case 9, with the most extensive degree of involvement and most severe retinal function impairment, had 20/50 vision in both eyes. All three patients had myopic corrections of more than four diopters.

*Severe impairment of peripheral retinal function*—Cases 10 and 11 had large ring scotomas, with some peripheral constriction in Case 10. Only small islets of peripheral field remained in Case 9. Dark adaptation was markedly elevated in all three patients, but most severely in Case 9. The ERG was extinguished in Case 9, showed only minimal responses at the highest intensities in Case 10, and was subnormal in Case 11 (Fig. 21).

## X-LINKED INHERITANCE

This category includes a condition known as choroideremia, progressive tapetochoroidal dystrophy and progressive chorioretinal degeneration.[8,30,31] It is our belief that X-linked choroidal sclerosis is the same condition as choroideremia. We will discuss evidence for the identity of X-linked choroidal sclerosis and choroideremia in this section.

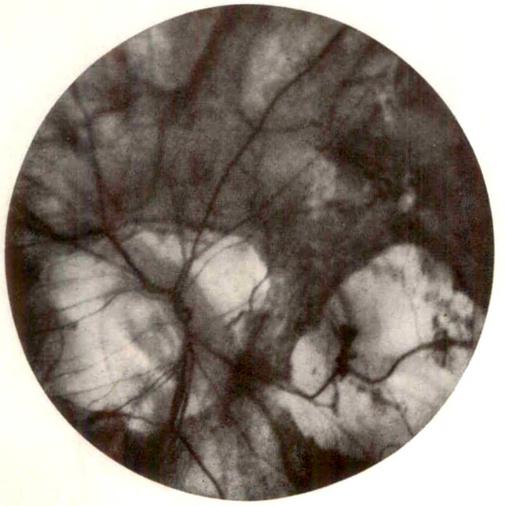


Fig. 13 (Krill and Archer). Case 6. Right posterior eyegrounds of a patient with malignant myopia. Discrete areas of total choroidal atrophy are evident around the optic disk and to its nasal side.

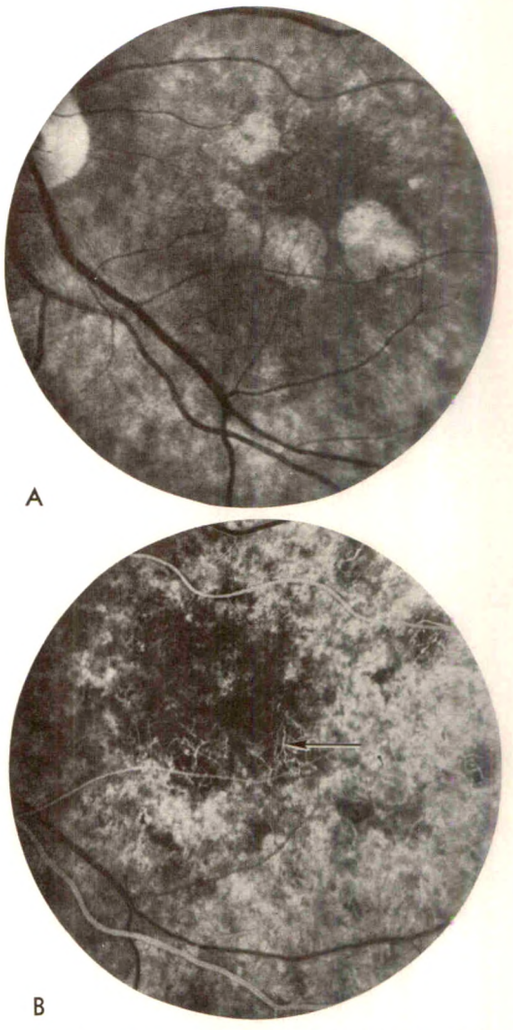



Fig. 14 (Krill and Archer). Case 7. Left macular area of a 36-year-old woman with an early form of diffuse choriocapillaris atrophy. (A) Several discrete areas of pigment epithelial and choriocapillaris atrophy are present at the macula. (B) Fluorescein angiography shows widespread hyperfluorescence typical of a pigment epithelial defect. At sites of choriocapillaris atrophy intermediate-sized choroidal vessels are visible (see arrow).

*Clinical features*—The onset of this condition is in the first decade, possibly in the first few years of life. Pigment epithelial stippling and atrophy in the equatorial and paramacular eyegrounds are seen initially. This

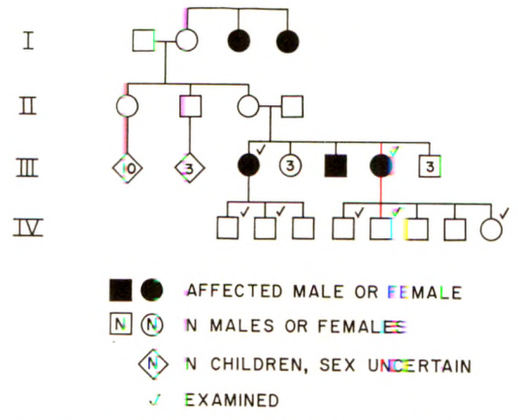



Fig. 15 (Krill and Archer). Pedigree of Cases 7 and 8 (diffuse choriocapillaris atrophy).

picture is similar to that noted in female carriers. Focal areas of choroidal atrophy with exposure of choroidal vessels represent the next stage of the disease. The areas of choroidal atrophy become larger and more numerous. Eventually most of the choroidal vessels disappear, leaving choroid only in the macula and scattered throughout the periphery. Clumps of retinal pigment are often seen in the equatorial retina. The retinal vessels may be attenuated in advanced cases.

Not all males will show the course described above. Frequently one or more males in a pedigree of known choroideremia will show eyegrounds with mainly choriocapil-

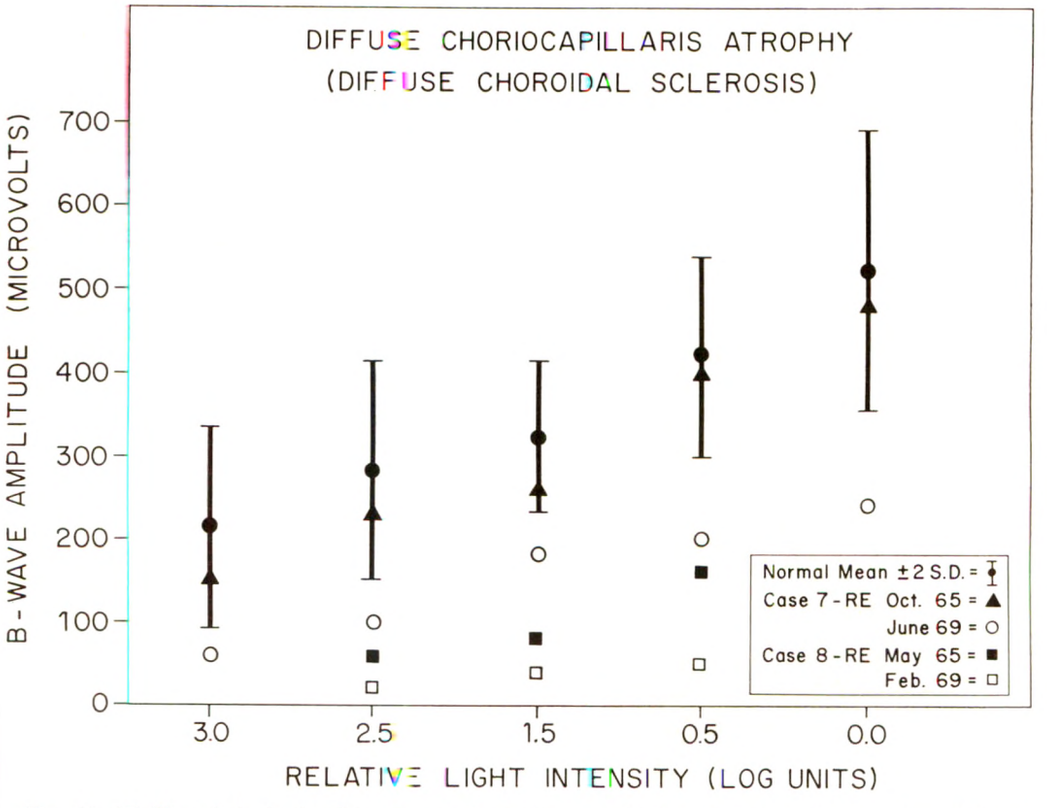



Fig. 16 (Krill and Archer). Cases 7 and 8. B-wave amplitudes plotted at three to five different intensities with normal control group. B-wave amplitudes are shown for the right eye in 1965 and 1969 from both patients. The ERG was initially normal in Case 7 (early disease), but by 1969 was definitely subnormal. In Case 8, with more severe involvement, the ERG was small in 1965 and almost extinguished in 1969.

laris atrophy,[30,31] and in such pedigrees, the disease is sometimes labeled X-linked choroidal sclerosis.[32] In fact, in some affected males some portions of the eyegrounds may show only choriocapillaris atrophy, and other portions total choroidal vascular atrophy.

*Retinal function*—Severe visual field constriction and night blindness are the first symptoms of the disease and occur at an early age. Visual acuity usually remains intact until at least the age of 30 years, but between the ages of 40 and 60, severe impairment of central acuity often occurs. Dark adaptation is markedly abnormal early in the disease, with relentless progression to severe night blindness. The ERG is subnormal in early cases and extinguished in advanced cases. The EOG is markedly abnormal in early as well as advanced cases.

*Histology*—Histologic studies have revealed extensive choroidal atrophy.[33] The only choroidal remnants were found at the macula and ora serrata. In these areas the walls of the choroidal vessels were thickened and lumina almost obliterated. In several areas Bruch's membrane had completely disappeared. The retinal vessels show atrophic changes as well.

Female carriers usually show eyeground changes.[34] These commonly consist of midperipheral pigmentation, localized deep in the retina, and spotty areas of pigment epithelial atrophy. The pigment may show clumping, particularly near the equator, and it is frequently distributed in a radiating pattern. Pigment in the macula may be fine and

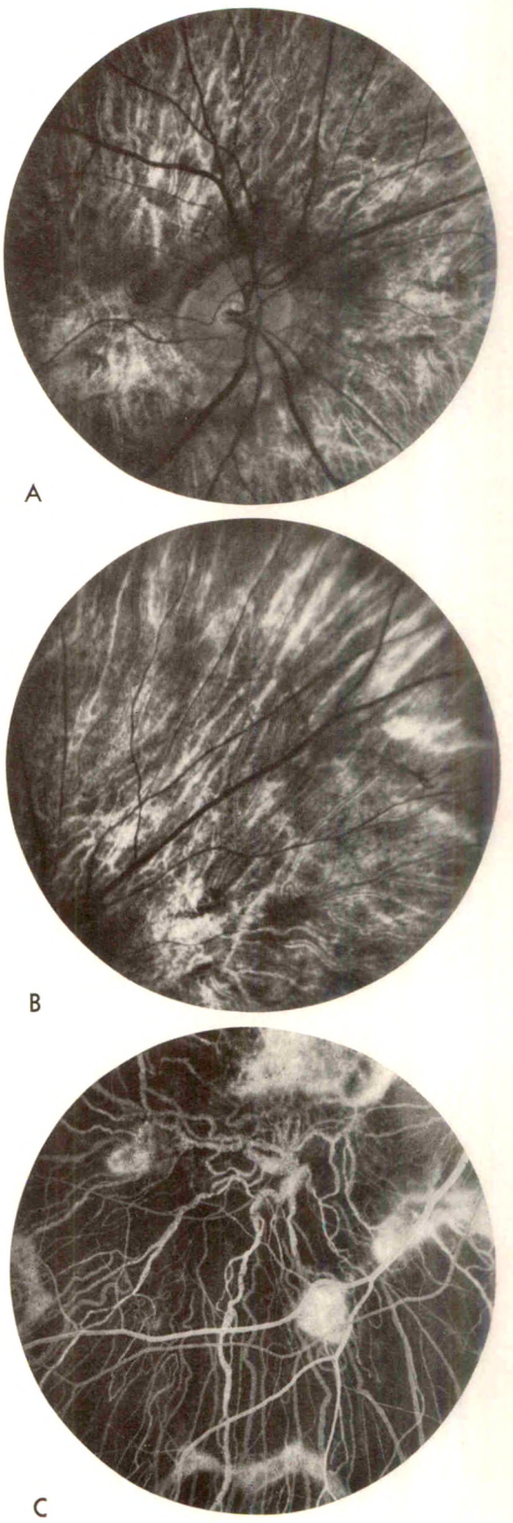



Fig. 17 (Krill and Archer). Case 8. (A) Posterior eyegrounds, and (B) periphery. There is pronounced visibility of the larger choroidal vessels in all areas. Many of the vessels are attenuated with whitish deposits along their course. Some even appear as thin white cords. (C) The larger choroidal vessels are visible throughout fluorescein angiography. Many of the choroidal vessels which appeared as white cords on ophthalmoscopic evaluation were patent to fluorescein.

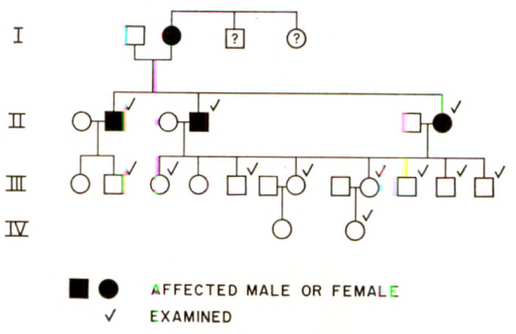



Fig. 18 (Krill and Archer). Pedigree of Cases 9, 10, and 11 (diffuse total choroidal vascular atrophy).

mottled. The optic disks and retinal vessels are usually normal. Occasionally, more extensive eyeground changes will be seen in the female intermediate between the typical carrier state and the fully affected male.[34] At least two females with a full form of the disease have been reported.[35,36] One carrier with typical eyeground changes was seen at the age of three and one-half years, but because the female does not show a progressive disease, it is possible that her changes were present at birth.

Occasionally, mild functional disturbances are noted, particularly dark adaptation. Abnormalities of the EOG and the ERG have been reported.[33]

Choroideremia has been described in great detail in a monograph on this subject.[30] The status of the female carrier has also been described in detail in another publication.[34] Only a few points will be made in this review, particularly in regard to eyeground changes.

## Case notes

Cases from pedigrees with known choroideremia described elsewhere[34] were chosen to illustrate the following points:

*Early disease in males*—A nine-year-old boy (Fig. 22) illustrates typical early eyeground changes. Note clumps of pigmentation and pigment epithelial atrophy in the midperipheral eyegrounds. The appearance is similar to that of female carriers (Fig. 23).

*Typical eyegrounds in carrier females*—The carrier usually shows pigment clumps in the equator and macula (Fig. 23-A) which tend to aggregate into larger clumps near the equator (Figs. 23-B and C). The pigment is often distributed in a striated or radiating pattern in the equatorial region (arrow in Fig. 23-B).

*Variation in degree of involvement in affected males*—This is well illustrated by a 20-year-old male who shows eyegrounds typical of choriocapillaris atrophy (Fig. 24-A). His 18-year-old brother shows changes typical of advanced choroideremia with total choroidal vascular atrophy (Fig. 24-B)

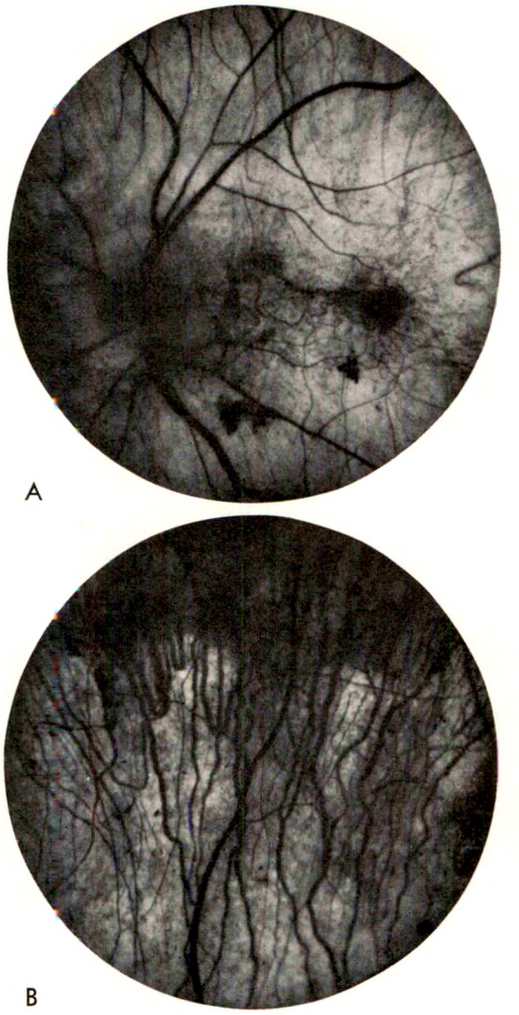



Fig. 19 (Krill and Archer). Case 9. (A) Posterior eyegrounds and (B) peripheral fundus, where there is a diffuse total choroidal vascular atrophy extending to the equator. A sharp transition zone with scalloped borders occurs at the junction of normal and involved areas.

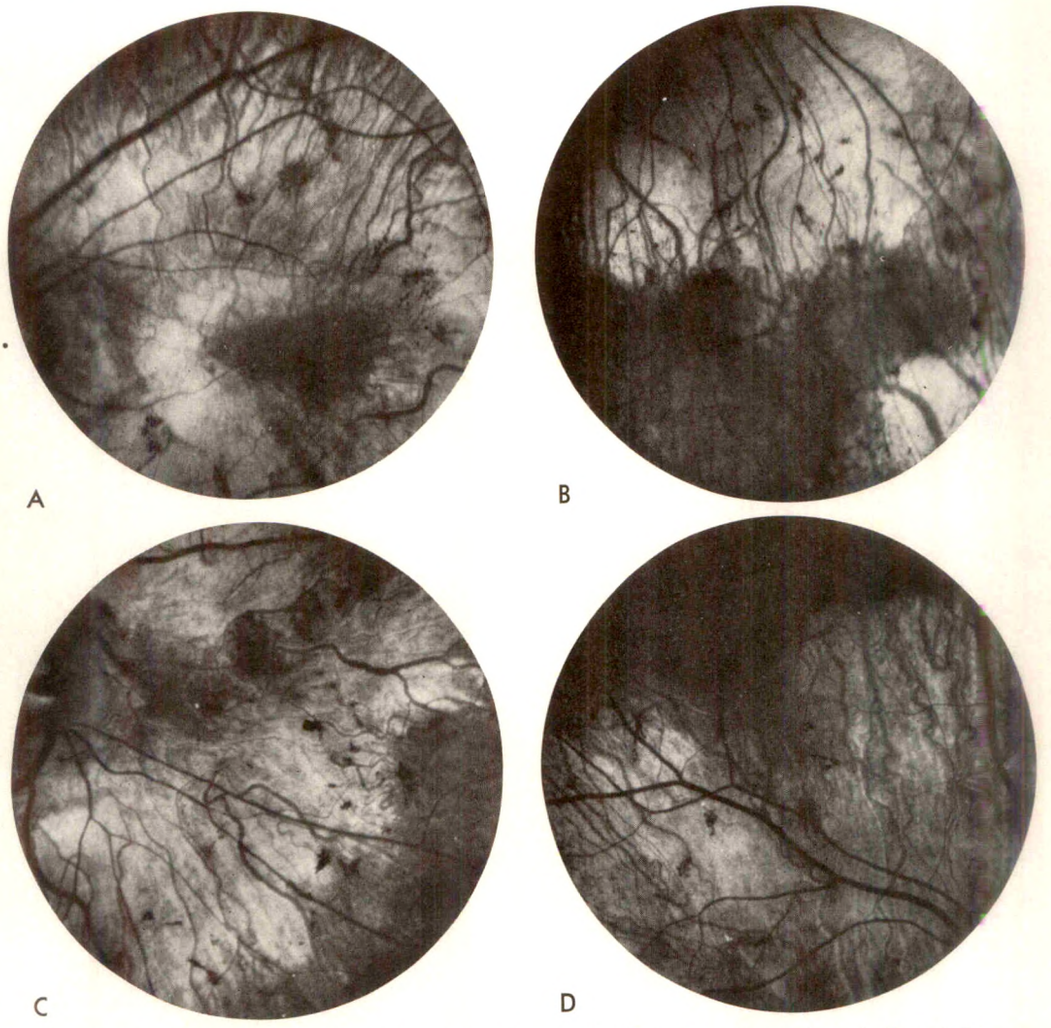



Fig. 20 (Krill and Archer). Cases 10 and 11. (A and C) Posterior eyegrounds and (B and D) preequatorial fundus. (B) Case 10 showed total choroidal vascular atrophy extending almost up to the equatorial area with sharp lines of demarcation. Notice the scalloped border. (C) Case 11 shows involvement confined mainly to the posterior eyegrounds. (D) Notice scalloped border of sharp demarcation line of a normal area and area of total choroidal vascular atrophy.

apart from the macula and far periphery. Obviously, the difference is not age-related.

This variability is also illustrated by three other affected male members from another family (Fig. 25). An 18-year-old male has the greatest degree of total choroidal vascular atrophy (Fig. 25-A). His 25-year-old uncle shows only choriocapillaris atrophy throughout most of his eyegrounds (Fig. 25-B). On the other hand, a 45-year-old uncle (brother of patient illustrated in Fig. 25-B) shows mainly choriocapillaris atrophy temporal to the disk (letter T in Fig. 25-C) and total choroidal vascular atrophy nasal to the disk (letter N in Fig. 25-C).

## Discussion

The choroidal vascular changes described in this paper are considered to be primary because of their progressive nature, the frequent evidence of a hereditary pattern, and the absence of toxic, traumatic, or inflammatory factors. The term "choroidal dystrophy" would apply to most of these conditions; however, as some of the cases lack evidence of a hereditary pattern, we

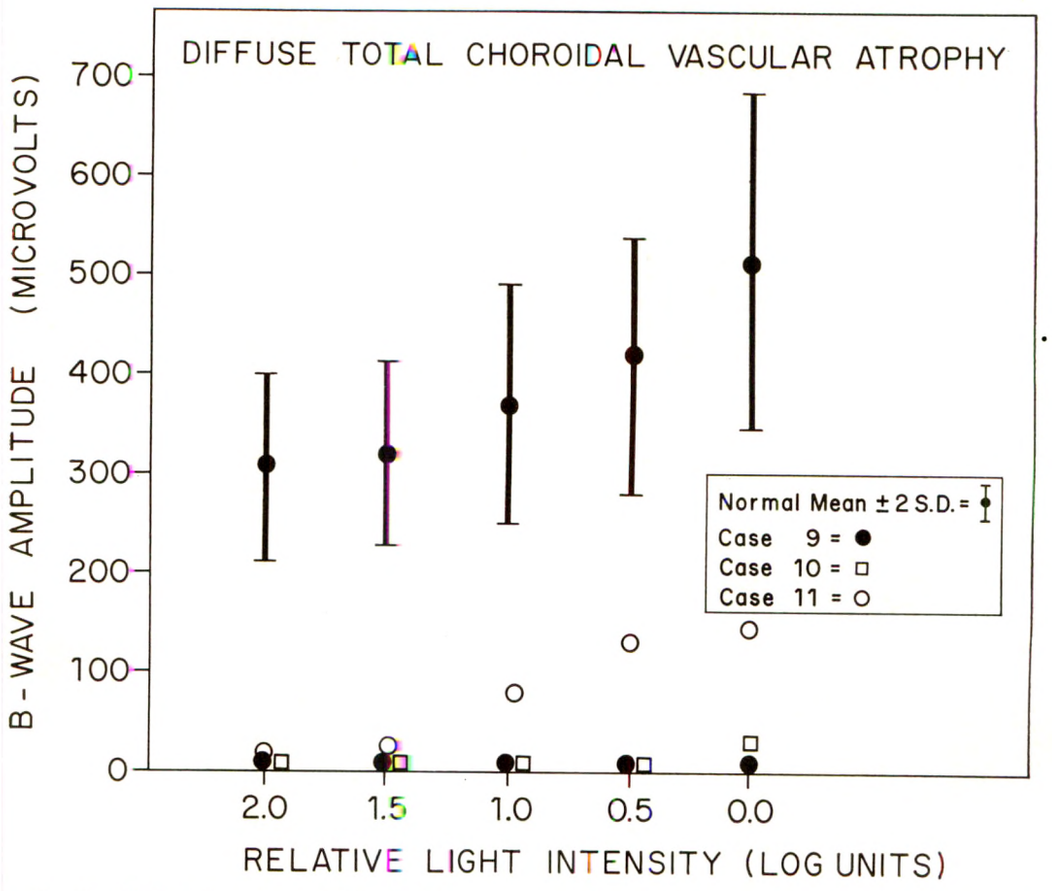


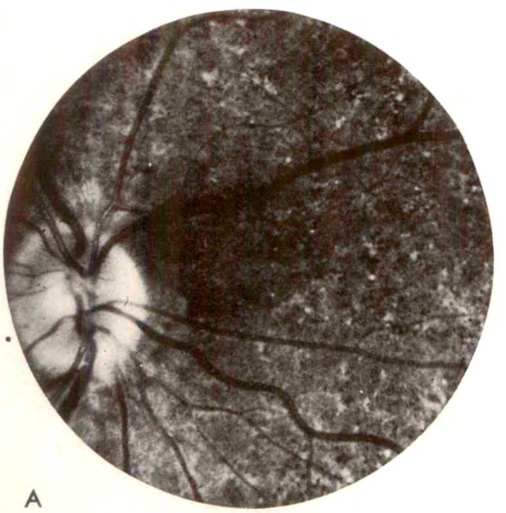

Fig. 21 (Krill and Archer). ERG of Cases 9, 10, and 11. Note extinguished records from Cases 9 and 10 and subnormal response from Case 11 with a lesser degree of involvement on ophthalmoscopic evaluation.

prefer to use the term "choroidal atrophies."

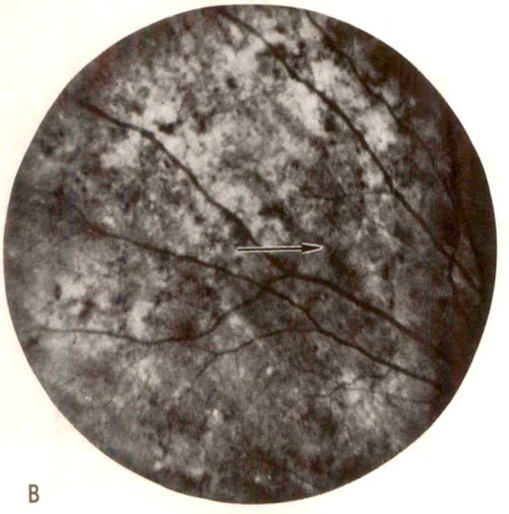
The cases described in this report have as their predominant feature atrophy of one or more layers of the choroidal vessels. In all instances, the vascular atrophy is associated with some measure of retinal pigment epithelial degeneration, in most cases corresponding precisely to the zone or focus of choroidal vascular change.



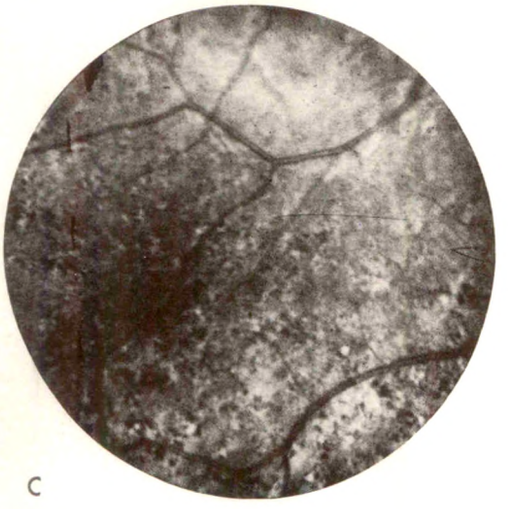
Fig. 22 (Krill and Archer). A nine-year-old with early choroideremia, illustrating the typical early eyeground changes seen in affected males. Pigment epithelial atrophy and clumping produce eyegrounds similar to those seen in the typical carrier female.



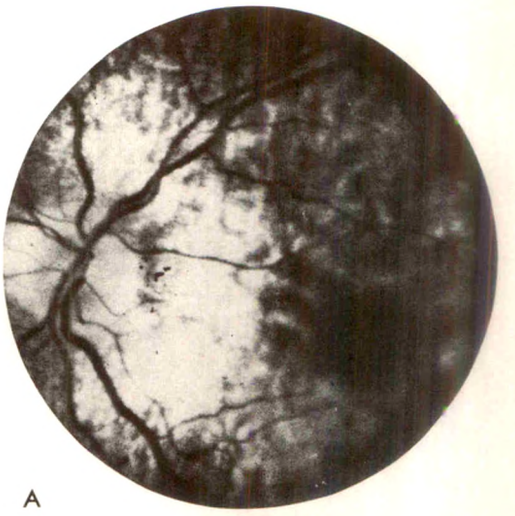
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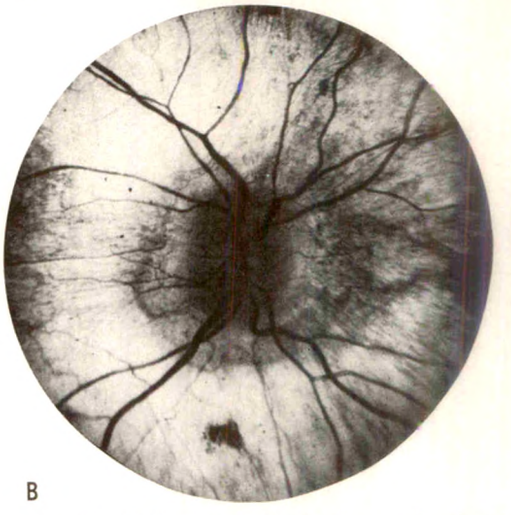
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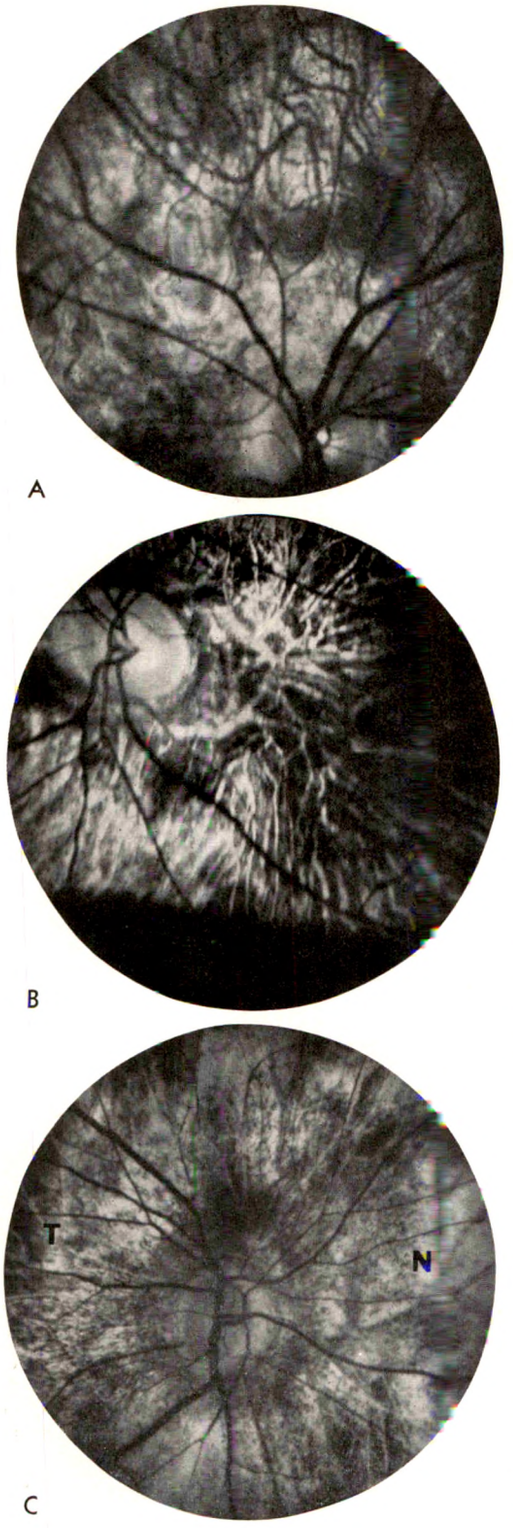
A



B

Fig. 24 (Krill and Archer). Two males from family with known choroideremia. (A) One, 20 years of age, shows choriocapillaris atrophy alone. Choriocapillaris atrophy is seen temporal to pronounced light reflex adjacent to disk. Note the white cord-like appearance of the larger choroidal vessels. (B) His 18-year-old brother has total choroidal vascular atrophy in all regions, apart from the macula and far periphery, typical of advanced choroideremia.

Fig. 23 (Krill and Archer). Three female carriers showing (A) typical changes at both equator and macula and (B) typical changes of pigment clumping at the equatorial fundus. (B and C). Large pigment clumps characteristically occur near the equatorial fundus. Striated or radiating patterns of pigment distribution may be noted at the equatorial region (arrow in Fig. B).




The choroidal atrophies, with certain exceptions, fall readily into two anatomic groups: those in which the atrophy is limited to the choriocapillaris, and those in which the larger choroidal vessels also disappear. The exception appears to be in choroideremia where both conditions may be seen in one eye, or where two members of an affected family show a different variety of the disease. However, in our experience, it seems that patients with choriocapillaris atrophy only rarely proceed to total choroidal atrophy, and patients with total choroidal atrophy continue to lose all vascular plexuses with progression of the disease.

Atrophy of the choriocapillaris and retinal pigment epithelium provides an unobstructed view of the large and intermediate-sized choroidal vessels. These vessels become surrounded by white deposits (probably by-products from the degenerating retinal pigment epithelium and choriocapillaris) which obscure the vessel lumen, and give the appearance of attenuated, cord-like or even totally obliterated vessels. The term "choroidal sclerosis" has been employed to describe these vessels. Fluorescein angiography has provided an accurate method of measuring luminal caliber, and most studies to date have indicated normal lumen size in the sclerotic vessels. Histologic studies also have shown no evidence of sclerosis. We thus recommend that the term "choroidal sclerosis" be abandoned.

The earliest changes leading to atrophy of the choriocapillaris appear to occur in the

Fig. 25 (Krill and Archer). Three male members of the same family showing variable degree of choroidal vascular atrophy. (A) An 18-year-old with a considerable degree of total choroidal vascular involvement. (B) A 25-year-old with only choriocapillaris atrophy throughout most of his eyegrounds. (C) A 45-year-old shows mainly choriocapillaris atrophy temporal to the disk (letter T) and large areas of total choroidal vascular atrophy nasal to the disk (letter N).

retinal pigment epithelium, as judged from early cases, extrapolization from changes occurring at the edge of an advancing lesion, and from relatives of patients affected with the overt disease. Pigment stippling and mottling are the characteristic ophthalmoscopic changes. Fluorescein angiography confirms the pigment epithelial defect and on occasion depicts small islets of choriocapillaris atrophy. We have not observed the retinal exudation and edema described by Sorsby and Crick[6] as the earliest changes in central areolar choroidal sclerosis, nor have we noted such changes at the border of an advancing lesion.

The difference between regional and diffuse choriocapillaris atrophy appears to be solely one of geographical extent. Both types of lesions have equivalent ophthalmoscopic and angiographic patterns, and appear to evolve in a similar fashion.

Visual field defects correspond to areas of obvious involvement on ophthalmoscopic evaluation. However, tests of diffuse retinal function, such as the ERG and EOG, show abnormalities that cannot be predicted from the extent of involvement noted in the eyegrounds. Optic atrophy and retinal vascular attenuation are usually indications of diffuse disease in those cases exhibiting a central lesion. In pedigrees with central choroidal atrophy, an occasional member may show much more widespread involvement, suggesting a further relationship between the regional and diffuse choriocapillaris atrophies.[8]

In the regional total choroidal atrophies the earliest changes are less well known. However, we have noted at the edge of expanding lesions a gray opacification located in the deeper retinal layers, obscuring all view of the underlying choroid. The retinal pigment epithelium eventually degenerates at this point, as evidenced by pigment clumping. In our series this finding is limited to the regional total choroidal atrophies, and has not been noted in the diffuse variety. Some workers feel that this disease represents an inflammatory process, and have designated the condition as geographic or serpiginous choroiditis.[16,37] We have not seen any evidence of inflammation in our patients. We feel that the slow, relentless progression is more typical of a degenerative process. In addition, retinal function evaluation frequently shows widespread impairment, despite the fact that most ophthalmoscopic changes are limited to the posterior eyegrounds. This finding also favors a degeneration rather than an inflammation. However, it is possible that such lesions may originate in either manner, and that we have not had the opportunity to see this type of patient. In the regional total choroidal vascular atrophies there appears to be a concomitant disappearance of small and large vessels; even the borders of advancing lesions reveal such changes. Fluorescein angiography shows that although vascular loss is extensive, it is rarely complete. Regional total choroidal vascular atrophies often have a distinct configuration. A serpiginous-like atrophy is seen at the macula, and the peripapillary atrophies typically show radial extensions emanating from the optic disk.

We feel that X-linked choroidal sclerosis is the same as choroideremia. In the original published pedigrees of X-linked choroidal sclerosis[32] there were males with typical eyegrounds of choroideremia and female carriers with eyegrounds identical to those described for choroideremia carriers. In our pedigrees with choroideremia, and those described by others,[30,38] there is great variability in the type of choroidal vascular atrophy which occurs. Atrophy of the choriocapillaris represents the earliest changes, but eventually atrophy of the larger vessels occurs. Both types of atrophy may at times be seen in the same eyegrounds of one individual with choroideremia, or different affected members of a family with this disease may show mainly one or the other type of choroidal vascular atrophy.

Variability in the total area of atrophy is fairly common in diffuse total choroidal vascular atrophy inherited in an autosomal dom-

inant manner, and, to a lesser degree, in choroideremia.

As stated previously, total choroidal vascular atrophies may result from primary diseases of the outer retina. Stargardt's macular degeneration, the cone degenerations, fundus flavimaculatus, and drusen may produce a choroidal, as well as retinal, atrophy in the macula in advanced stages. Degenerative, or arteriosclerotic disease of the larger choroidal vessels may precipitate choroidal hemorrhage and consequential choroidal atrophy. An inflammation can produce choroidal atrophy.

Small regional areas of choroida atrophy outside the macula, particularly of the choriocapillaris, may be seen with retinitis pigmentosa.[39] The choroideremia carrier may show total choroidal vascular atrophy around the optic disk. A toxin, such as thioridazine, may produce a diffuse choriocapillaris atrophy.[24]

Enhanced visibility of the choroidal vasculature may result from pigment migration and loss in otherwise normal retinal pigment epithelial cells. This is a not uncommon finding in myopic persons and aged individuals, and has been labeled depigmentation in situ by Klien.[40] These fundi may be differentiated from those with choriocapillaris atrophy by normal vision, retinal function studies, and fluorescein angiography.[12]

## Summary

At attempt is made to classify the primary choroidal vasculature atrophies. The patients can be divided into those with mainly choriocapillaris atrophy and those with atrophy of the large choroidal vessels as well. The atrophies can also be divided according to extent of involvement into regional and diffuse choroidal vascular atrophies.

All diseases, except choroideremia, have either atrophy of only the choriocapillaris or atrophy of all sized choroidal vessels in early as well as advanced stages. Only one disease, choroideremia, shows both types of atrophy.

Unique configurations are seen in the regional total choroidal vascular atrophies and in the autosomal forms of diffuse total choroidal vascular atrophy, known as gyrate atrophy of the choroid and retina.

Many of the regional choroidal vascular atrophies showed evidence of more widespread impairment on functional evaluation.

It is likely that most, if not all, of the conditions discussed could be considered genetic in origin and therefore labeled as dystrophies. We speculate that the primary abnormality in all of the choroidal atrophies of genetic origin is probably in the pigment epithelium.

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# BILATERAL INFLAMMATORY PSEUDOTUMORS OF THE CILIARY BODY

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Non-neoplastic inflammatory pseudotumors have been reported to arise at extraocular sites within the orbit[1-3] as well as in the posterior uveal tract.[4-7]* Since their clinical appearance was indistinguishable from that of a malignant melanoma of the choroid, psuedotumors presenting as intraocular masses have been treated by enucleation and their true nature was not apparent until histologic examination of the eye had been performed.

The case that is presented here is the first to our knowledge in which intraocular inflammatory pseudotumors presented initially as bilateral masses of the anterior uvea. This report illustrates that a nonspecific inflammatory process, reactive lymphoid hyperplasia, may reach large proportions suggesting the diagnosis of tumor. Thus, such a pseudotumor should be considered in the differential diagnosis of mass lesions of the anterior uveal tract. This case is of additional interest because of the patient's striking response to corticosteroids administered systemically as compared to the topical or subconjunctival route.

## CASE REPORT

A 51-year-old white man was referred to the Wilmer Institute for evaluation of a ciliary body mass in the right eye. He had enjoyed excellent health except for mild, bilateral neural hearing loss of long duration and unknown etiology. His ocular history was unremarkable save for a number of corneal foreign bodies which were removed without incident followed by uneventful recovery. He had worked in the coal mines of West Virginia and, more recently, he was employed as foreman of a machine shop.

Two months prior to admission, he consulted his ophthalmologist in West Virginia because of the onset of pain and redness in the right eye. His vision was noted to be RE:20/40, and LE:20/20. The right eye showed injection of the bulbar conjunctiva, 1+ ray and cells, and granular keratic precipitates. The patient was given neomycin/polymyxin B, plus 0.1% dexamethasone eye drops every two hours, homatropine drops twice daily, and oral prednisolone, initially 20 mg per day, tapered over a four-day period and then discontinued. Although the topical corticosteroids were continued, no improvement occurred over the next six weeks, and once again a course of systemic prednisolone, 5 mg/daily, was given for one week. At this time increased vascularity of the iris was noted, and a mass which extended circumferentially around the peripheral iris and ciliary body from six to 12 o'clock was seen for the first time. Because of the possibility that this lesion might represent a melanoma of the iris and ciliary body, he was referred to Wilmer.

On initial examination at Wilmer, best corrected vision in the right eye was 20/60 and in the left eye 20/40. The bulbar conjunctivae of both eyes were moderately injected. The pupil of the right eye was irregular and poorly reactive due to numerous posterior synechiae. Granular keratic precipitates and 2+ ray and cells were present bilaterally with 1+ cells in the vitreous. Early nuclear and moderately advanced posterior subcapsular lens opacities were present in the right eye. An unusual circumferentially oriented, nonpigmented mass was seen to elevate the peripheral iris from six to 12 o'clock in the right eye. Where the iris stroma was thinned peripherally, the mass had a pinkish coloration and seemed to have a gelatinous consistency. Dilated blood vessels traversed the mass in a radial direction. Slit lamp examination of the iris of the left eye revealed no abnormalities. Gonioscopic examination of the right eye demonstrated the iris root to be pushed well away from the trabecular meshwork as though by a posterior mass extending from six to 12 o'clock. The ciliary cleft was very deep and broad, giving almost the appearance of angle recession. Markedly dilated circumferential and radial vessels traversed this cleft. The remaining half of the angle, from 12 to six o'clock, appeared normal with a Grade III approach (Fig. 1). Gonioscopic examination of the left eye demonstrated a similar appearance of the angle from the 12 to the three o'clock position, but there was no evidence of a

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* Beasley[4] initially considered his case to be a solitary choroidal lymphosarcoma. Zimmerman,[6] however, later reviewed the sections and concluded that the lesion was inflammatory and not malignant in nature.

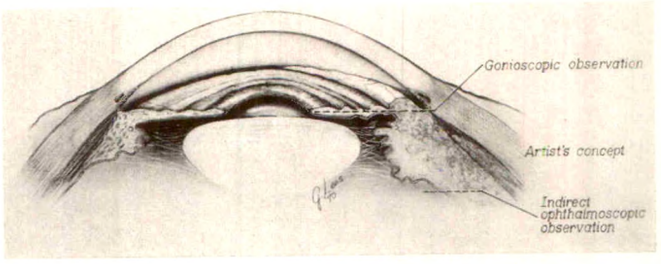



Fig. 1 (Ryan, Frank, and Green). Artist's conception of the appearance of the chamber angle of the right eye at the time the patient was initially presented to Wilmer. A large, ring-shaped mass elevates the peripheral iris in the temporal half of the eye. The greater arterial circle of the iris is dilated, and dilated vessels, arising from the greater circle, traverse the mass and run over the iris in a radial direction toward the pupil. The nasal half of the iris and angle appear relatively normal.

mass and no abnormal vessels were observed. Over the remaining 270 degrees in the left eye, the chamber angle was normal. Intraocular pressures were 14 mm Hg bilaterally, and examination of the fundi with the indirect ophthalmoscope and scleral depression revealed no abnormalities. However, examination with the slit lamp and the Goldmann three-mirror prism contact lens demonstrated posterior and inward displacement of the ciliary processes and pars plana by the mass from six to 11 o'clock in the right eye. Transillumination demonstrated a normal transscleral pattern with no defect posterior to the ora serrata.

An exhaustive systemic evaluation performed in conjunction with our medical consultant, Dr. Leigh Thompson, was normal except for the physical signs of emphysema. While exhibiting equivocal changes, quantitative assay of immunoglobulins revealed no significant elevation or depression. Multiple cytologic examinations of sputum were negative for tumor cells.

Cytologic examination of aqueous obtained by paracentesis of the right eye demonstrated only mononuclear inflammatory cells, mostly lymphocytes, and a few histiocytes. No neoplastic cells were evident. A biopsy of the conjunctiva from the fornix of the right eye revealed normal tissue. Biopsy of a scalene lymph node showed mild reactive hyperplasia, and percutaneous liver biopsy revealed scattered foci of mononuclear inflammatory cells but no indication of tuberculosis, fungal disease or sarcoidosis. "Bone-free" radiographic studies[8] of the anterior segment of both eyes showed no evidence of radiopaque foreign bodies.

Since this extensive evaluation gave no clue as to the nature of the ocular lesion, and in particular because it failed to differentiate between an inflammatory process and primary or metastatic intraocular malignancy, direct biopsy of the ciliary body was undertaken. A modified Stallard-type incision[9–11] was made over the ciliary body, with the circumferential cut extending from eight to 11 o'clock and the radial incision at right angles to this in the nine o'clock meridian. Upon retracting the scleral flaps, a gelatinous mass involving the ciliary body was encountered (Fig. 2). A wedge of tissue was removed for histologic examination.

Hematoxylin-eosin stains of the tissue demonstrated a diffuse, moderately cellular chronic inflammatory infiltrate, consisting of plasma cells, lymphocytes, and a few histiocytes (Fig. 3). No multinucleated giant cells were present, and there were no plasma-cytoid cells or Russell bodies. Several dilated blood vessels and ciliary muscle fibers were seen, and no necrosis was evident. Special stains for bacteria, fungi, and acid-fast organisms were negative, as were stains for iron. Periodic acid-Schiff (PAS) stained sections demonstrated no intranuclear, PAS-positive inclusions.[12]

It was concluded that the patient had an inflammatory pseudotumor of the ciliary body of the right eye, and probably a similar lesion at an earlier stage of development in the left eye. The pathogenesis of these lesions remained undetermined. Because of the inflammatory nature of the ocular disease, it was elected to treat the patient with 60 mg of oral prednisone daily, covered with 300 mg of isoniazid (INH) and antacids. Topical 1.0% prednisolone

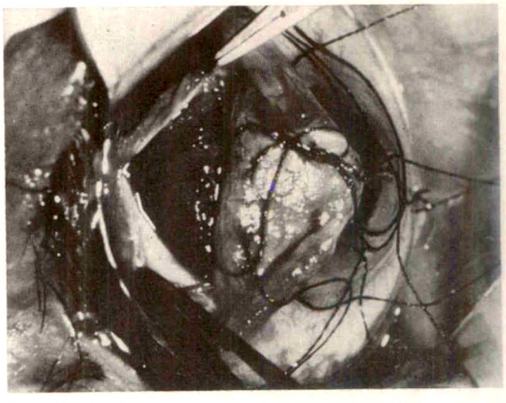


Fig. 2 (Ryan, Frank, and Green). Appearance of the mass in the ciliary body of the right eye at the time of surgery. Forceps retract the edges of the radial arm of the T-shaped cyclectomy incision. The mass, which had a pinkish coloration, appears dark in this photograph and lies between the retracted flaps.

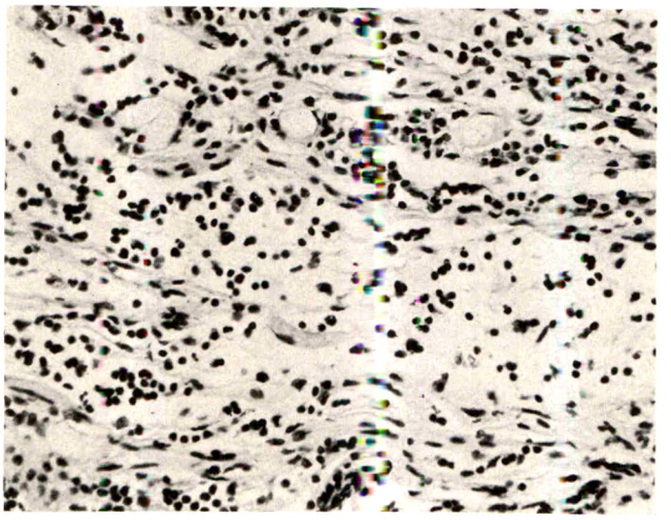


Fig. 3 (Ryan, Frank, and Green). Representative field from a section of the ciliary body biopsy from the right eye. Mononuclear inflammatory cells including lymphocytes and rare plasma cells are present. No giant cells are found, and there is no necrosis. Note blood vessels and ciliary muscle fibers. The lesion is much less cellular than pseudotumors of the posterior uvea which have been reported previously[4-7] (hematoxylin-eosin, ×370).

acetate to both eyes every three hours and 3% atropine twice daily were continued.

The response of the ocular lesions to this therapy was prompt. The cellular reaction in the vitreous the ray and cells in the anterior chamber, and the keratic precipitates disappeared, initially in the less severely affected left eye and eventually in the right eye. One month following the patient's discharge from the hospital, the gonioscopic appearance of the chamber angle in the left eye was normal, and during the second month after discharge the prominent vessels disappeared from the iris and angle of the right eye. The ciliary body mass was much less in evidence, and the region of the angle from six to 12 o'clock demonstrated changes suggestive to atrophy of the ciliary body and an appearance similar to that of angle recession. Visual acuity at this time was RE:20/60, and LE:20/20-3, and tensions were 8 and 17 mm Hg, respectively. Because of marked weight gain and a Cushingoid habitus, the systemic corticosteroids, which had been maintained at 60 mg/day for two months, were tapered over a two-month period and then discontinued. One month later the topical corticosteroids to the left eye were stopped. The patient returned the following month, however, with a one-week history of redness and decreased visual acuity in the left eye. Vision was RE:20/200, and LE:20/60 intraocular pressures were 3 and 9 mm Hg, respectively, with granular keratic precipitates and marked ray and cells in the anterior chamber of the left eye. Only minimal inflammatory signs without keratic precipitates were present in the right eye. Gonioscopically the angle of the right eye was unchanged, while in the left eye there were now many widely dilated radial and circumferential vessels in the temporal and most prominently in the inferior quadrants of the angle (Fig. 4). There was a moderate outpouring of cells in the anterior vitreous of both eyes, but again no abnormalities were noted on detailed fundus examination.

The frequency of topical corticosteroid administration was increased and, in order to provide a higher local corticosteroid concentration, as well as to minimize the possibility of systemic side effects, dexamethasone was injected subconjunctivally in 4 mg doses. One week later the dilated vessels had virtually disappeared from the angle in the left eye, leaving an atrophic appearance, but there was an

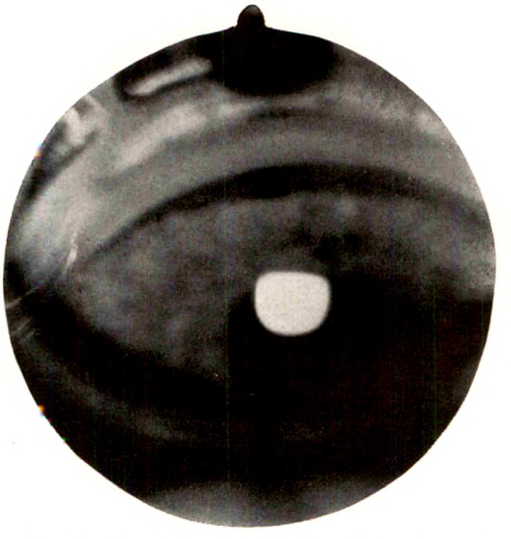


Fig. 4 (Ryan, Frank, and Green). Goniophotograph of the inferior quadrant of the chamber angle of the left eye during a relapse. Dilated blood vessels arising from the greater circle of the iris are seen in the angle. These occurred during relapse and resolved on oral prednisone therapy. The blurred appearance of the photograph is due to the intense anterior chamber reaction.

increased cellular reaction in the right eye and new vessels in the inferior quadrant of the angle. Hourly topical corticosteroids were continued and over the next two weeks the patient received five doses of subconjunctival dexamethasone to each eye. Visual acuity did not improve and the signs of inflammation persisted on this form of therapy, however, and oral prednisone, 60 mg/daily, was begun. Once more there was a prompt response. One week after starting the oral corticosteroids vision was RE:20/200, and LE:20/30. The cellular reaction in the anterior chamber had diminished, although many vitreous cells remained in both eyes, tensions were RE:6 mm Hg, and LE:14 mm Hg, and the chamber angle of both eyes now displayed a recessed appearance with the iris root drawn centrally and a deepened ciliary cleft (Fig. 5). No vessels were evident. The patient was maintained on oral prednisone, 60 mg every other day, along with topical prednisolone and atropine, and oral INH and antacids, until the inflammation once again became quiescent.

In order to prevent a rebound, systemic corticosteroids were tapered by very small increments. There was slow progression of the bilateral cataracts. Potentially contributing factors for both lenses were the anterior segment inflammation and systemic corticosteroid therapy. The right eye, in addition to the possible direct effects of cyclectomy, had presistent hypotony postoperatively; when vision in this eye had been reduced to hand motions, and to 20/80-1 in the left, cataract extraction was advised. While receiving 40 mg prednisone per day, the lens was removed uneventfully.

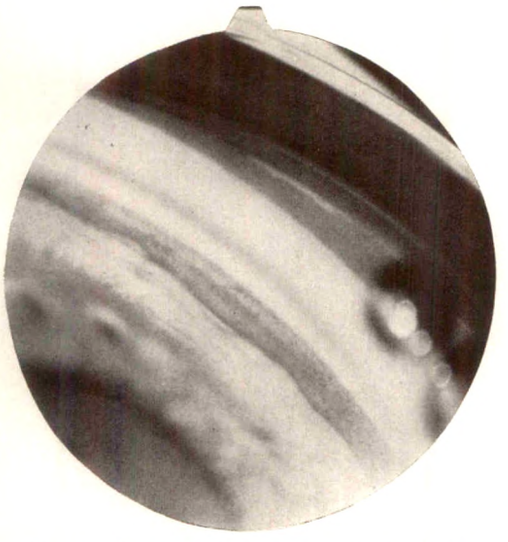


Fig. 5 (Ryan, Frank, and Green). Goniophotograph of the temporal quadrant of the chamber angle of the left eye 15 months after initial presentation and following remission of the inflammatory process on cortirosteroid therapy. All angle structures are easily seen, and the ciliary cleft appears markedly deepened, as in traumatic recession of the angle. No mass is evident, and there are no abnormal blood vessels.

Two weeks postoperatively visual acuity was 20/200 in the right eye with a +10.00 and pin hole. Intraocular pressure was 6 mm Hg with a 1-2+ ray and cells and anterior vitreous debris. Systemic corticosteroids are now being slowly tapered. The left eye exhibits posterior subcapsular cataract and moderate iris atrophy.

Continued medical evaluation has demonstrated no evidence of systemic disease. Serum protein electrophoresis, done while systemic corticosteroids were being tapered, disclosed mild hypogammaglobulinemia. Three immunoglobulin assays, done one month apart while corticosteroids were being tapered and two months after they were discontinued, showed moderate decrease of IgG, in the range 570-660 mg% (normal, 900-1500 mg%) with normal IgA and IgM. A Kveim test, performed during a period when the patient was off systemic corticosteroids, was negative. Despite the negative results of his repeated thorough physical and laboratory evaluation, he is presently followed with the awareness that some associated systemic disease may be diagnosed in subsequent years.

## Discussion

When dealing with a patient who presents with a mass in the anterior segment, the clinician must consider a variety of possibilities.[7,13,14] These include several types of neoplasms, both primary and metastatic, infectious granulomata (e.g., tuberculosis or syphilis), those of presumably noninfectious origin (e.g., sarcoidosis), and a reaction around an encysted and previously unsuspected intraocular foreign body. Finally, one must consider various disorders of the serum proteins such as Waldenstrom's macroglobulinemia.

In the present case, the bilaterality of the disease process (although a mass was initially prominent only in the right eye) made certain of these diagnostic possibilities less likely. For example, our patient's occupational history and his history of multiple corneal foreign bodies suggested to us that an intraocular foreign body might be the source of his difficulties, but it would be most remarkable for foreign bodies to be present in bilaterally symmetrical locations, or for a single one to cause bilateral anterior inflammation. Similarly, primary ocular tumors

(except retinoblastoma) are almost invariably unilateral.

On the other hand, involvement is bilateral in 20-25% of metastatic ocular tumors, according to several series cited by Reese.[13] Occult carcinomas of the lung may present with anterior ocular lesions before the primary site has been discovered.[15-17] For this reason, and because our patient had some clinical evidence of pulmonary disease, we were particularly anxious to exclude this possibility. Tumors primary in other organs may also metastasize to the eye,[15-17] and this consideration was important in our evaluation. Lymphomas may involve orbital and ocular tissues, including the anterior segment,[13] although according to Zimmerman,[6] "Most of the obviously malignant lymphomas of the orbit occur in patients who already have an established diagnosis or who present other evidence of systemic involvement."

Infectious and other systemic inflammatory disorders are, of course, relatively frequent causes of bilateral ocular lesions. An infectious basis is not likely in view of the exhaustive systemic evaluation and histologic appearance of the ciliary body and other biopsy specimens. Similarly, evidence for sarcoidosis was lacking in all biopsy material as well as in chest x-ray films, and a Kveim test was negative. Relatively mild and inconstant abnormalities of serum immunoglobulins have been demonstrated, but in over 18 months of follow-up there has been no evidence of systemic disease. The possibility remains, of course, that such a disorder might become apparent at a later date.

Blodi and Gass,[5] in their discussion of inflammatory pseudotumors of the orbit, note that bilateral involvement is unusual, but when it occurs, a relatively high percentage of these patients later show manifestations of systemic disease, most notably Wegener's granulomatosis, lymphomas, or leukemias. Little[18] has recently described a patient with Waldenstrom's macroglobulinemia who developed bilateral masses in his lacrimal glands. Biopsy of one of these lesions revealed a histologic picture similar to that in the present case, except that Little was able to demonstrate numerous PAS-positive intranuclear inclusions in the lymphocytes and plasma cells. Moreover, there had been a long history of prior disease, with tissue considered to be lymphomatous in the wall of the patient's stomach and in a mass behind the urinary bladder. There was also significant elevation of serum gamma globulins and of the IgM peak on immunoelectrophoresis. Such cases emphasize the need for close medical follow-up of patients with inflammatory pseudotumors.

This report documents the value of cyclectomy as a biopsy procedure. While certainly not a procedure to be taken lightly, iridocyclectomy has been used increasingly in recent years to excise malignant[9,10] and (where the preoperative diagnosis was uncertain) benign[11] tumors of the iris and ciliary body without necessitating loss of an eye. Its efficacy and safety seem to be moderately well established. When used for diagnostic purposes only, it need hardly be emphasized that cyclectomy should not be done unless appropriate attempts have been made preoperatively to establish a diagnosis by other means.

Finally, it is worth commenting on the rapid response of this inflammation to corticosteroid therapy. Intraocular pseudotumors which have been reported previously[4-7] have presented as lesions of the posterior uveal tract, and have eventually been treated by enucleation because they were suspected to be malignant melanomas of the choroid. If the inflammatory mass lesions in the present case bear any similarity to those discussed in the past, then their response to corticosteroids lends weight to the suggestion of Gass[5] that suspicious lesions of the posterior uvea might merit a diagnostic trial of corticosteroid therapy before enucleation. Since such lesions, whose neoplastic nature is clinically uncertain, are usually "treated" by an initial period of watchful waiting, the addition of

high-dose corticosteroids during this interval may be beneficial. If such a diagnostic/therapeutic approach is taken, the clinician must remain fully cognizant that some neoplasms (e.g., the lymphomas and the inflammatory components of others) can show a dramatic response to systemic corticosteroids.


## Summary

A 51-year-old man presented with bilateral ciliary body masses associated with signs of iridocyclitis. The differential diagnosis included malignant melanoma, lymphoma, metastatic tumor, and granulomatous inflammation of the ciliary body. After an exhaustive systemic evaluation to rule out extraocular disease, diagnosis was made by biopsy of the ciliary body. The lesion proved to be a nonspecific inflammatory process, consisting of numerous lymphocytes, plasma cells, and histiocytes. There was a good response to systemic corticosteroid therapy.



## Acknowledgment

We thank Harry T. Linger, M.D., of Clarksburg, West Virginia, for referring this patient to us.


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# UNUSUAL COURSE OF A CILIARY BODY MELANOMA

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Extrabulbar extension of uveal melanomas is usually associated with a grave prognosis.[1] However, this communication presents a follow-up report of an unusual case, originally reported by Hogan,[2] of ciliary body melanoma which presented as an epibulbar pigmented nodule and pursued a remarkably benign course for 19 years.

## CASE REPORT

A 37-year-old white woman was first examined by an ophthalmologist in December, 1960, for a pigmented lesion of the sclera (Fig. 1) which had remained unchanged for the preceding 10 years. The scleral lesion was grey, 4 mm in diameter, and located 5 mm posterior to the superior limbus in the vertical meridian. The lesion was neither elevated nor vascularized. On gonioscopic examination, a tumor mass was detected in the angle in a position corresponding to the location of the scleral lesion (Fig. 2). The ciliary body was unremarkable, and the visual acuity and intraocular pressure were normal. The pupil was of normal size and shape and dilated normally. Examination in 1961 demonstrated no change in the findings. In 1962, the scleral lesion was slightly elevated and had increased to a diameter of 10 mm. At this time, a smooth, slightly elevated ciliary body tumor was noted which corresponded to the site of the scleral lesion. There was no further change until 1969, when progressive growth of the ciliary body and angle tumor became obvious (Figs. 3 and 4). The extrascleral extension at this time measured 5 mm in diameter. The apparent decrease in size since 1962 was attributed to loss of pigment. The patient was referred to the University of California, San Francisco, for consultation and the eye was enucleated on October 23, 1969.

*Pathology*—Gross examination revealed a pigmented ciliary body tumor superiorly which was contiguous with a nonpigmented peripheral iris angle tumor. A black pigmented epibulbar tumor measuring 5 mm in diameter was present near the limbus overlying the intraocular tumor.

On microscopic examination, a tumor was seen arising from the ciliary body superiorly and extending into the chamber angle (obliterating the angle) and iris root (Fig. 5). The tumor extended via

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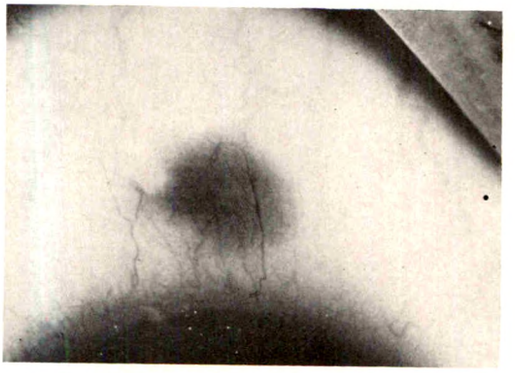


Fig. 1 (Matas). Scleral pigmented lesion—1960 (UCEP-69-692).

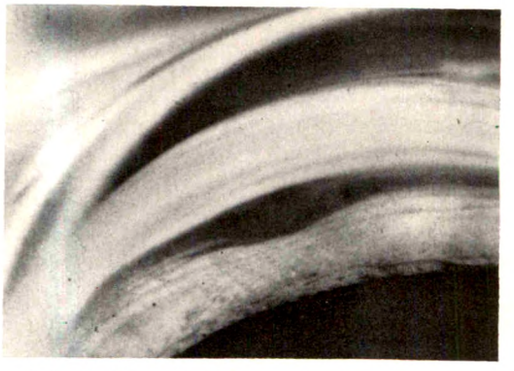


Fig. 2 (Matas). Gonioscopic view of angle tumor—1960 (UCEP-69-692).

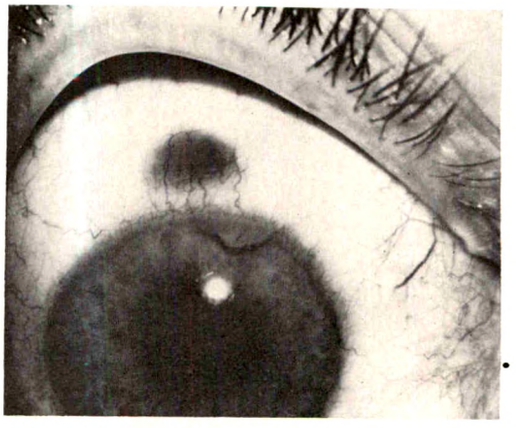


Fig. 3 (Matas). Sclera pigmented lesion—1969 (UCEP-69-692).

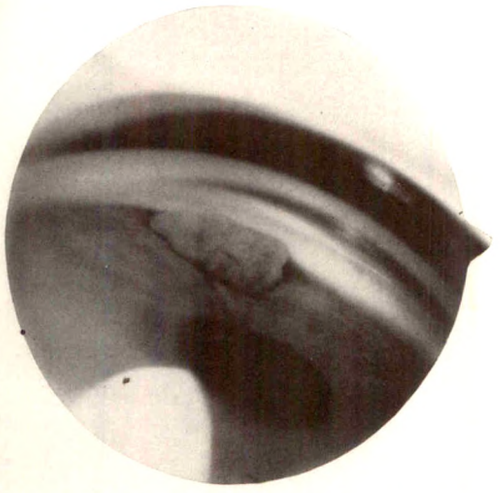


Fig. 4 (Matas). Gonioscopic view of angle tumor—1969 (UCEP-69-692).

scleral channels to give rise to an episcleral mass near the limbus (Fig. 6). The episcleral tumor had a fibrous capsule.

The tumor was lightly pigmented and consisted largely of cohesive, spindle-shaped cells with hyperchromatic nuclei and prominent nucleoli. The cellular cytoplasm was relatively scanty.

The diagnosis was melanoma of the ciliary body and angle, spindle cell B type,[3] with epibulbar extension.

## Comment

This case is of interest because of its unusual course in which the ciliary body melanoma was present as an extrascleral extension for 19 years before the tumor could be clinically detected within the ciliary body. At the time of enucleation the patient was asymptomatic and without the usual clinical features[4,5] associated with ciliary body melanomas. It is unusual for a pigmented epibulbar mass to be the initial finding of a ciliary body or choroidal melanoma, but occasionally such cases are reported.[6] The prognosis is generally considered to be compromised by extrascleral extension. In the series reported by Starr and Zimmerman,[7] the five-year mortality rate in cases with extrascleral extension was 66% compared to 33% in cases without extension. This difference in mortality may be partially explained by the apparent tendency of the more malignant cell types (epithelioid, necrotic, mixed) to extend more frequently than do spindle cell tumors. The cell type of the ciliary body tumor reported here was spindle B, a finding that is perhaps related to the unusually slow progression of this lesion over a period of so many years.

## Summary

In a case of ciliary body melanoma with extrabulbar extension, both the presentation and subsequent course were unusual. The tumor cell type was spindle B, considered to be less malignant than the mixed or epithelioid cell types that are more frequently associated with extrabulbar extension. There was a 19-year interval in this case between the appearance of the scleral pigmented lesion and the subsequent enlargement of the ciliary body tumor. The slow growth of this ciliary body tumor may be related to the tumor cell type.

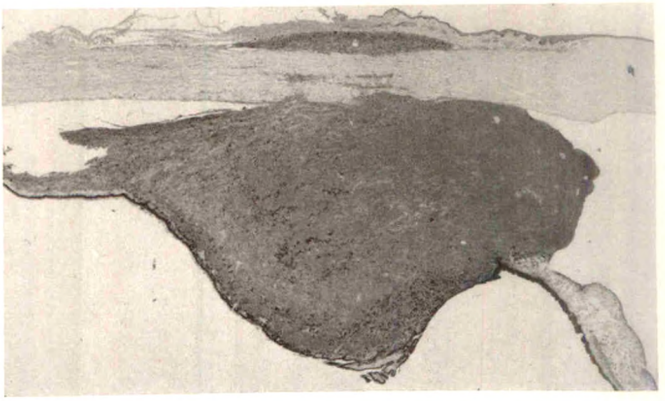


Fig. 5 (Matas). Ciliary body melanoma, showing extension into the anterior chamber angle and extrascleral extension (hematoxylin and eosin, ×11) (UCEP-69-692).

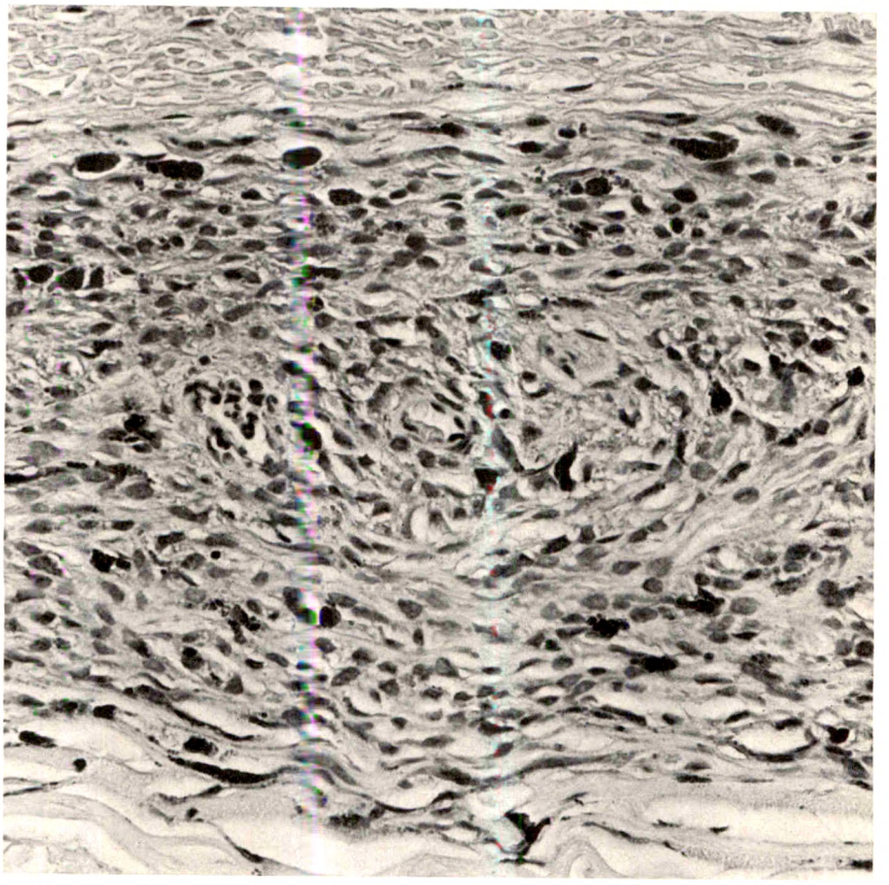


Fig. 6 (Matas). High power view of extrascleral extension of ciliary body melanoma (hematoxylin and eosin, ×400) (UCEP-69-692).

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# CONJUNCTIVAL MALIGNANT MELANOMA ORIGINATING IN ACQUIRED MELANOSIS SINE PIGMENTO

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Malignant melanomas of the conjunctiva are encountered infequently.[1] Clinical significance is based upon the high mortality rate (about 40%) and the usual necessity of exenterating the orbit.[2] The pathogenesis of conjunctival malignant melanoma is attributed to two antecedent melanotic lesions: conjunctival nevi and acquired conjunctival melanosis. Some melanomas arise de novo without such antecedent lesions.[3] The case reported here is attributed to an unusual and apparently previously unreported form of acquired melanosis.

## CASE REPORT

The patient, a 54-year-old white man, was first admitted to the Wilmer Institute of the Johns Hopkins Hospital on January 14, 1970, for treatment of multiple pigmented nodules within the medial portion of the right upper eyelid (Fig. 1). The nodules had been noted three weeks prior to admission. Eight months previously, a malignant melanoma had been excised from the medial bulbar conjunctiva and caruncle of the right eye.

Ocular examination revealed a visual acuity of 20/15 in each eye. There was a well-healed, slightly hypertrophic scar of the medial bulbar conjunctiva of the right eye. Two small, lightly pigmented nodules were palpable within the deep tissues of the upper eyelid of this eye medially. These nodules could be seen through the skin and conjunctiva, neither of which was ulcerated. The rest of the conjunctiva appeared unremarkable. The remainder of the ocular examination—including ocular motility, slit-lamp examination and ophthalmoscopy—disclosed no abnormalities. No palpable lymph nodes could be found. A careful general examination, including roentgenologic and extensive liver function studies, revealed no evidence of distant metastatic disease.

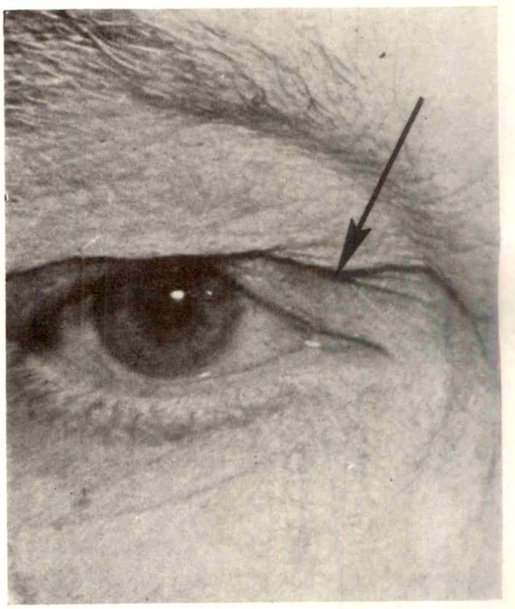


Fig. 1 (Griffith, Green, and Weinstein). Preoperative appearance, showing pigmented nodules (arrow) which are partly obscured by redundant upper eyelid. No conjunctival pimentation is visible.

The clinical impression was locally recurrent malignant melanoma of the conjunctiva. Several attending ophthalmologists at the Wilmer Institute, and two visiting physicians who are distinguished in the field of ocular oncology (Zimmerman and Blodi) concurred with this diagnosis. In the absence of any discernible conjunctival pigmentation, a diagnosis of antecedent acquired melanosis was not entertained.

Examination of sections from the original resection, obtained from the patient's local hospital, confirmed the diagnosis of malignant melanoma of the conjunctiva and also disclosed features of acquired melanosis both of which were similar to the more recent material.

On January 23, 1970, under general anesthesia, a biopsy of the lesions, using immediate frozen sections, revealed malignant melanoma (Fig. 2), and a complete exenteration of the right orbit was then performed. The bony socket was lined with split-thickness skin graft from the thigh. The postoperative course was uneventful. Eleven months later, however, an enlarged lymph node developed in the

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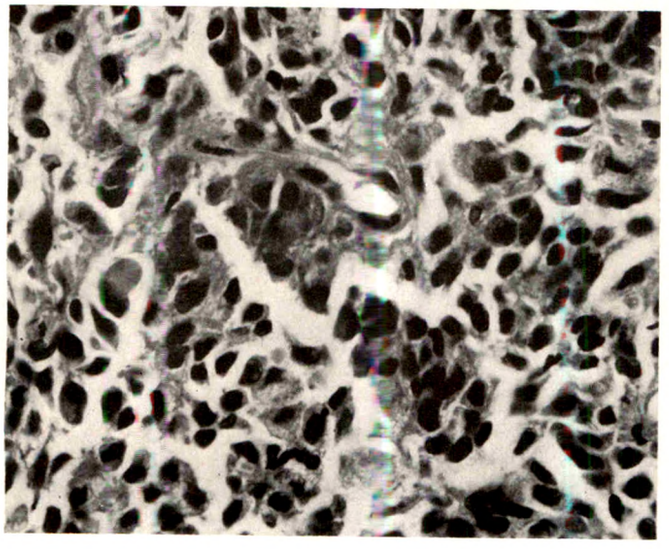


Fig. 2 (Griffith, Green, and Weinstein). Surgical biopsy specimen from right upper eyelid. Highly anaplastic tumor cells with cytoplasmic melanin granules are seen (hematoxylin and eosin, ×700).

right cervical area. This node was excised and disclosed metastatic melanoma.

*Pathology*—Gross examination of the exenterated tissue revealed a specimen measuring 55 × 45 × 48 mm, consisting of the right eyelids and orbital contents. An 8 mm horizontal biopsy incision was present in the upper eyelid nasally. Periosteum was generally intact. Within the upper eyelid and inferior to the biopsy incision several lightly pigmented nodules were found, the largest of which measured 5 mm in diameter. No further neoplasm was seen. The conjunctiva was free of pigmentation. Vertical sections were taken.

On microscopic examination, the neoplasm was seen to occupy almost the complete thickness of the medial upper eyelid, involving the upper tarsal border, levator aponeurosis, substantia propria of the upper forniceal conjunctiva, and the external aspect of Tenon's capsule (Fig. 3). Sheets and clumps of spindle and epithelioid cells formed the neoplasm. The epithelioid cells in particular were quite anaplastic, with three or four mitotic figures per high-power field. Moderate amounts of intracellular melanin granules were seen in the central areas of the tumor. Along some margins, a lymphocytic infiltrate was seen.

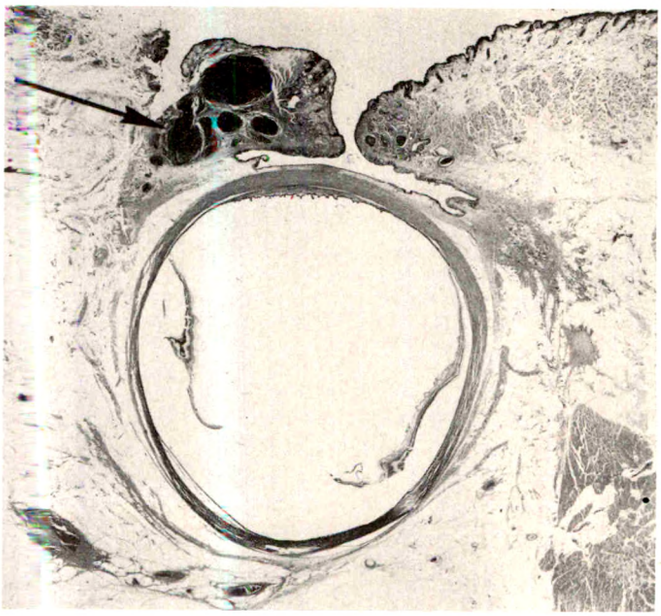


Fig. 3 (Griffith, Green, and Weinstein). Vertical sections of medial portion of exenteration specimen, showing the biopsy incision and tumor nodules (arrow) in the upper eyelid (hematoxylin and eosin, ×2.5).

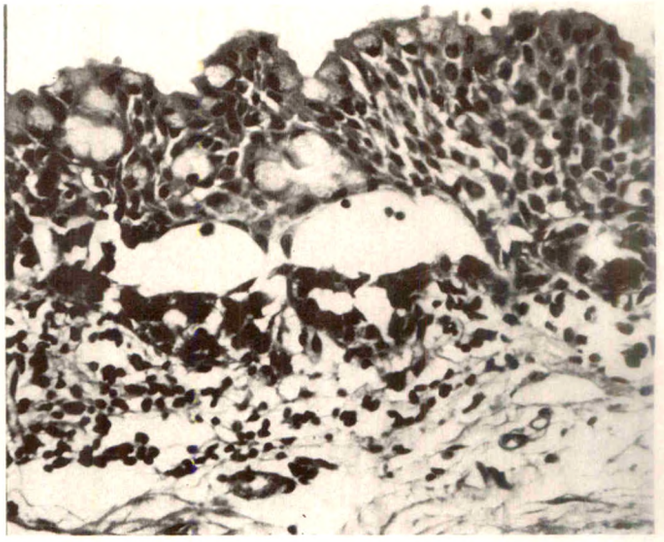


Fig. 4 (Griffith, Green, and Weinstein). Inferior bulbar conjunctiva. Nests of hyperchromatic, melanin-free cells are seen at the epithelial junction, with subjacent inflammatory infiltrate (hematoxylin and eosin, ×290).

Widespread areas of intense junctional activity were present and involved the bulbar, upper and lower foniceal and upper and lower tarsal conjunctiva. These areas consisted of nests of mildly pleomorphic cells with hyperchromatic nuclei (Fig. 4). Nests of similar cells containing more abundant, vacuolated cytoplasm and eccentric and hyperchromatic nuclei were also seen. An intense mononuclear inflammatory response was present in the substantia propria adjacent to some of these areas (Fig. 5). No pigment granules were seen in these areas of junctional activity, either in the hematoxylin-and-eosin-stained sections or in those stained by the Fontana silver impregnation technique.

The globe was unremarkable. The margins of the total specimen were well clear of the neoplasm, and no further neoplastic deposits were seen deeper in the specimen. A careful search showed no evidence of lymphatic invasion.

The diagnosis was: locally recurrent malignant melanoma of the conjunctiva originating in amelanotic acquired melanosis of the conjunctiva.

## Comment

It has been known since the turn of the century[4,5] that acquired melanosis of the skin can lead to malignant melanoma. Appreciation by ophthalmologists that a similar

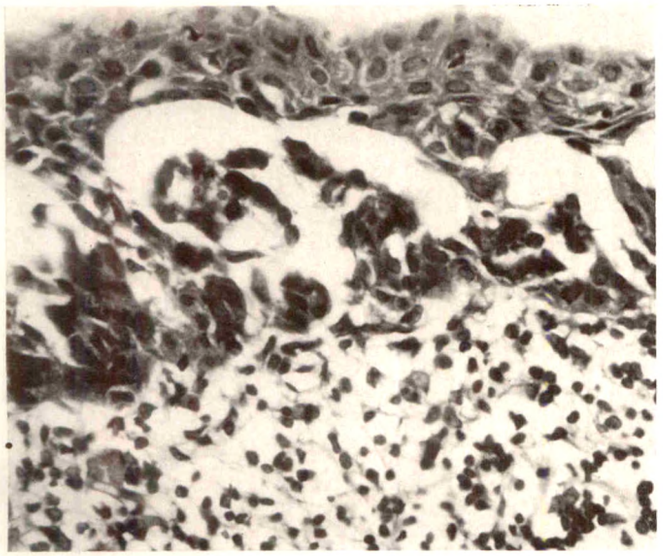


Fig. 5 (Griffith, Green, and Weinstein). Inferior forniceal conjunctiva. Nests of melanin-free, pleomorphic, hyperchromatic cells occupy the junctional zone. An intense inflammatory response is present in substantia propria (hematoxylin and eosin, ×390).

process can occur in the conjunctiva is due mainly to the writings of Dr. Algernon Reese. His early papers, based in part on cases from the literature, suggested that malignant transformation was a constant feature of acquired melanosis of the conjunctiva. The resulting malignant melanomas seemed, also, to have a uniformly bad prognosis; therefore, aggressive therapy during the precancerous stage seemed indicated.[6,7] Subsequently, his continuing interest in this condition and meticulous long-term observation enable Dr. Reese to assemble a large personal series of cases of malignant melanoma of the conjunctiva. His 1966 paper,[2] in which he described 83 cases of precancerous melanosis (42 with follow-up exceeding five years) and 62 cases of cancerous melanosis (36 of which were followed five years or longer), remains the definitive clinical study. Dr. Reese reported that precancerous melanosis progressed to cancerous melanosis in 17% of cases. The 36 cases of cancerous melanosis had a mortality rate of 40%.

There was a striking variability, however, in the clinical courses of both lesions. To quote Dr. Reese[2]: "The erratic course of precancerous and cancerous melanosis in contrast to the constant and predictable course of uveal melanomas makes the selection of treatment most difficult. . . . In general, an exenteration is indicated when it can be established that the tumor has advanced to the cancerous stage."

Other reports, although based on smaller series and often with less follow-up, seem to be in general agreement with Reese.[3-10]

Lederman[11] reported good results using primary radiation therapy for selected conjunctival malignant melanomas. However, he did not advocate radiation therapy during the precancerous stage. A recently reported study[12] from the Memorial Hospital, New York, reviewed 1483 cases of cutaneous malignant melanomas in an attempt to assess the value of lymph node dissections performed routinely. However, neither conjunctival melanomas nor head and neck melanomas were analyzed separately.[12]

There is some controversy as to the relative importance of the two types of antecedent lesions. Reese[13] has attributed two-thirds of conjunctival malignant melanomas to precancerous or acquired melanosis, and he attributed the remaining third to conjunctival nevi. Zimmerman,[3] citing his own experience at the Armed Forces Institute of Pathology, found that the antecedent lesion could not be determined in one-half of the cases. Of the remainder, two-thirds were attributable to nevi and one-third to acquired melanosis.

Of what significance is the present case? Dr. Reese's original paper, as well as the other reports cited, stress that acquired melanosis of the conjunctiva is a diffuse, nonelevated, pigmented lesion, with the melanin pigment often having a somewhat granular distribution. The diffuse nature of the condition was emphasized, suggesting that junctional activity may extend beyond the obvious areas of pigmentation. Nonetheless, increased pigmentation was the crucial diagnostic feature.

Our case suggests that, in the complete absence of such pigmentation, a clinical diagnosis may be all but impossible, with the junctional activity being appreciated only upon biopsy and histologic examination. This may be termed "acquired melanosis sine pigmento," analagous to retinitis pigmentosa sine pigmento. Certainly, whenever a melanotic lesion is excised, the margins of the specimen should be carefully examined for evidence of acquired melanosis. Where such examination is inconclusive, further conjunctival biopsies, even of nonpigmented areas, would be valuable.

Final understanding of this puzzling condition will require both accurate initial histologic diagnosis and long-term follow-up.

## Summary

A case of malignant melanoma of the conjunctiva arising from clinically unrecognized acquired melanosis is described. Clinically,

no conjunctival pigmentation was observed. Histopathologic examination of the exenteration specimen disclosed widespread junctional melanocytic activity characteristic of acquired melanosis. No melanin was observed in the areas with routine and special staining techniques.

Acknowledgments

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Ophthalmic miniature

Of old when folk lay sick and sorely tried
The doctors gave them physic, and they died
But here's a happier age: for now we know
Both how to make men sick and keep them so.

Hilaire Belloc
On Hygiene

# REPORT OF A CASE OF SPHENOID FISSURE SYNDROME STUDIED BY ORBITAL VENOGRAPHY

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The sphenoid fissure syndrome arising from inflammation surrounding the cavernous sinus or the superior orbital fissure is a condition with many synonyms: painful ophthalmoplegia,[1,2] orbital apex syndrome,[3] superior orbital fissure syndrome,[4] Tolosa-Hunt syndrome,[2] or superior orbital fissuritis.[5] The etiology of the inflammatory process has not been determined. The purpose of this paper is to describe a case of sphenoid fissure syndrome in which occlusion of the superior ophthalmic vein was demonstrated by orbital venography.

## CASE REPORT

A 15-year-old black girl, a high school student, presented on August 22, 1969, at the University of Texas Medical Branch Hospitals complaining of pain in her left eye and was admitted for further evaluation. Four weeks earlier, the patient noted a left-sided headache and this was followed two weeks later by progressive diplopia. There was no history of trauma, recent upper respiratory infection, previous headaches or earaches, or any syncopal episodes or seizures. She had a gonococcal genitourinary infection six months prior to the onset of her symptoms.

The visual acuity was 20/20 in the right eye and 20/30-1 in the left. Intraocular pressure by applanation tonometry was 10 mm Hg on the right and 16 mm Hg on the left. Hertel exophthalmometer readings with a base of 105 mm were 16 mm on the right and 19 mm on the left. Blepharoptosis was present on the left. There was paralysis of the fourth and sixth nerves, and partially of the third (Fig. 1). The right eye was normal. The pupil was 3 mm in diameter in both eyes and they reacted to light and accommodation equally. The conjunctiva, cornea, anterior chamber, and lens were normal in both eyes. No evidence of venous stasis was observed. The fundi were normal. Peripheral visual fields by Goldmann perimetry were normal. The remainder of the physical examination, including neurologic evaluation, was within normal limits.

Chest, skull, and sinus radiograms were normal. A thorough laboratory study, including $^{3}$Tm resin uptake and fluroescein treponema antibody test, was normal. A spinal tap revealed no cells; glucose, 59 mg%; protein; 25 mg%, and chloride, 124.5 mEq. A carotid arteriogram revealed no lesions.

Orbital venography (Fig. 2) performed via the frontal vein demonstrated occlusion of the left su-

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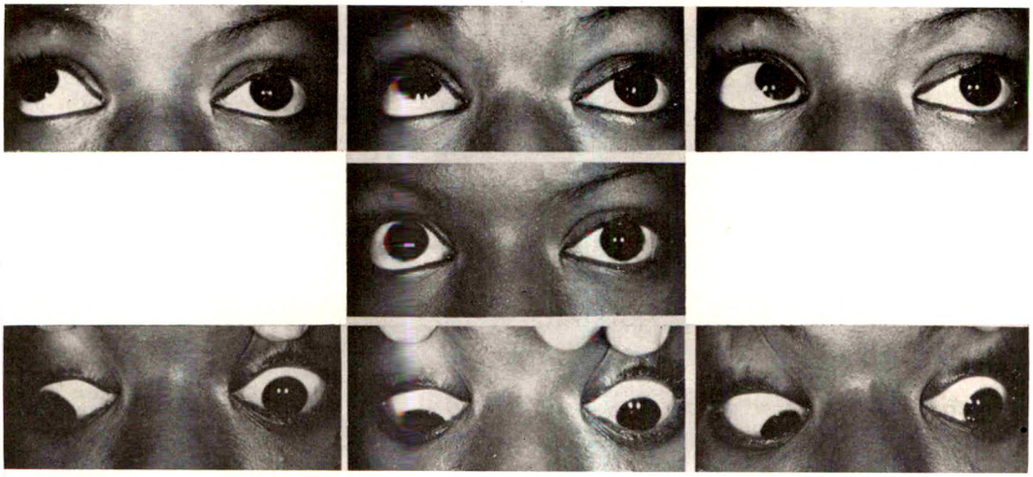


Fig. 1 (Milstein and Morretin). Pretreatment demonstration of blepharoptosis, and partial third, fourth, and sixth nerve paralysis.

perior ophthalmic vein in the superior orbital fissure with no displacement of the vessel suggestive of obstruction by a mass. No filling of the left cavernous sinus was noted. On September 3, the patient was started on prednisone, 60 mg daily. By September 5, the patient's headaches ceased, and a day later, improvement of lateral rectus function was noted. Over a two-week period, the patient gradually regained full extraocular muscle function and was discharged on September 23 with no residual ophthalmoplegia and with a final visual acuity of 20/20. Repeat orbital venography at the completion of treatment demonstrated a patent superior ophthalmic vein with filling of the cavernous sinus (Fig. 3).

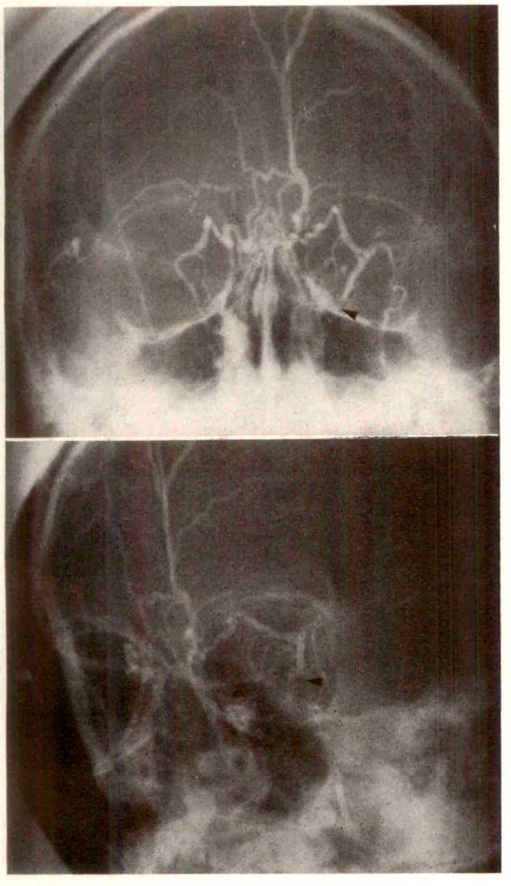


Fig. 2 (Milstein and Morretin). Orbital venogram. Top: Frontal view. The left ophthalmic vein is slightly dilated and tapers progressively to the point of obstruction (arrows) at the superior orbital fissure. The cavernous sinus is opacified on the right side (normal) and not on the left side. Bottom: Oblique view. The lumen of the obstructed superior orbital vein is irregular. Note the small collateral venules adjacent to the obstruction.

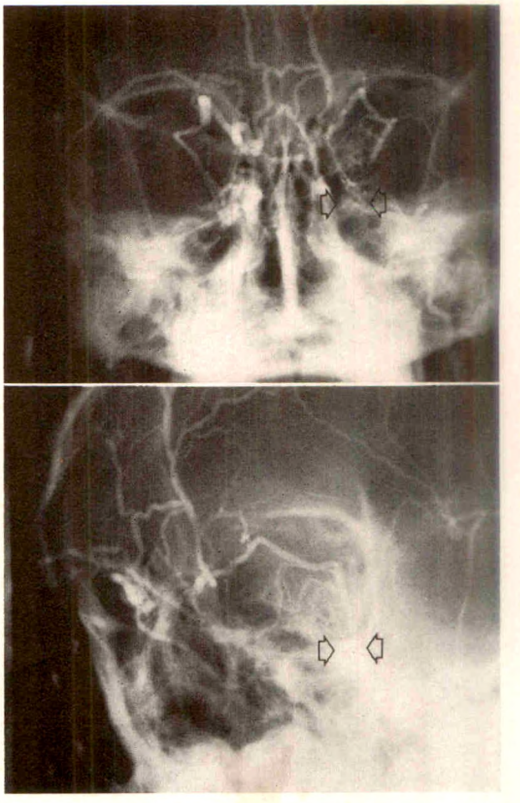


Fig. 3 (Milstein and Morretin). Repeat orbital venogram after treatment. Top: Frontal view. Bottom: Oblique view. The left superior ophthalmic vein, although still narrowed, is patent. The left cavernous sinus is now opacified (arrows).

## Discussion

The etiology of superior orbital fissure syndrome has been attributed to: (1) aneurysm of the internal carotid artery at the posterior communicating junction, (2) neoplasm, (3) carotid cavernous fistula, (4) gummatous periostitis about the orbital fissure, (5) meningovascular syphilis with oculomotor palsy, and (6) trauma.[5] Other causes of superior orbital fissure syndrome include ophthalmic migraine and diabetes mellitus. Diabetic third nerve palsy typically does not include pain as a significant symptom. The patient presented in this study demonstrates an additional etiology recognized by previous authors—inflammation of the sphenoid fissure or the cavernous sinus.[2-6]

Painful ophthalmoplegia was originally described in the French literature in 1865.[7,8] In 1896, Rochon-Duvigneaud named this constellation of symptoms and signs "le syndrome de la fente sphenoidale," or the sphenoid fissure syndrome.[7] More recently, in 1954 Tolosa[9] described a man with superior orbital fissure syndrome in whom a pathologic study of the cavernous sinus revealed granulomatous tissue which surrounded, but did not completely obstruct, the lumen of the cavernous sinus.

Seven years later, Hunt and associates[6] reported six cases of retro-orbital pain and involvement of the structures lying within the cavernous sinus and its walls. Lakke[4] reported a similar case in which he included a rather extensive review of the literature on the superior orbital fissure syndrome. He found local pachymeningitis in the area of the cavernous sinus.

In 1966, Smith and Taxdale[2] described five cases of painful ophthalmoplegia and its excellent response to systemic corticosteroids, an observation also made by Hunt and associates,[6] indicating that indolent inflammation of the cavernous sinus or the sphenoid fissure was the etiology.

Retro-orbital pain is one of the earliest and most constant symptoms of the sphenoid fissure syndrome, as seen in the present case. Limitation of ocular movements usually follows. The superior rectus muscle is generally the first to lose its function.[4]

The present case is similar to the one reported by DeJean,[3] Holt,[3] Tolosa,[9] Hunt,[6] and Smith[2] in that: (1) pain preceded the ophthalmoplegia, (2) neurologic involvement included the third, fourth, fifth, and sixth cranial nerves, (3) the symptoms lasted for weeks, and (4) extensive studies, including angiography, demonstrated no lesions outside the cavernous sinus. Hunt[6] and Smith[2] both felt that spontaneous remissions occur, some with residual deficits, and that attacks may recur.

The present case is unique in that this syndrome has rarely been recorded in a patient so young. It is also the only case to document, by orbital venography, occlusion of the superior orbital vein and then its patency after treatment. Venography established a tentative diagnosis of a localized inflammatory process because of the tapering characteristics of the obstruction of the superior ophthalmic vein and the irregular lumen of this vessel. It was felt that orbital venography supported the impression that this was not neoplastic since the vein showed no displacement (Fig. 2). As previous investigators have found, the etiology of the inflammation remained obscure.

Occlusion of the superior ophthalmic vein does not help to establish the etiology of this rather bizarre inflammatory disease of the sphenoid fissure and cavernous sinus, but it is a useful diagnostic technique. Every effort should be made in cases of painful ophthalmoplegia to discover an etiology and to rule out malignancy. When this has been done, the suggestion by Hunt[6] and Smith[2] that these patients be treated with systemic corticosteroids seems most prudent and effective.

## Summary

A 15-year-old black girl was seen with painful ophthalmoplegia of four weeks' duration. Two weeks earlier, blepharoptosis had occurred which was followed by progressive paralysis of the third, fourth, and sixth nerves with pupillary sparing. Orbital venography via the frontal vein established occlusion of the superior ophthalmic vein as a concomitant finding. Treatment with prednisone was followed by complete regression of signs and symptoms within two weeks.

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OPHTHALMIC MINIATURE

The colour metamorphosis of the sea was studied by the Undersea Research Group. We took down colour charts with squares of pure red, blue, yellow, green, purple, orange, together with a range of greys from white to black, and photographed the chart at various levels down to the twilight zone. At 15 feet red turned pink, and at 40 feet, became virtually black. There, also, orange disappeared. At 120 feet yellow began to turn green, and everything was expressed in almost monochromatic colours. Ultraviolet penetrated quite deeply, while infrared rays were totally absorbed in inches of water.

J. Y. Cousteau
*The Silent World*
London, Hamish Hamilton, 1953

# SCANNING ELECTRON MICROSCOPY OF THE LENS AND ZONULAR FIBERS

ARTHUR E. OBERMAN, M.D.
*Los Angeles, California*

Application of scanning electron microscope techniques offers startling photographs of surface features of biological materials. Due to the great depth of field, several hundred times greater than by transmission electron microscopy and optical microscopy, a three-dimension-like picture is obtained. Resolution of surface features is limited only by fixation techniques of the specimen and electron beam damage to the surface at higher magnifications. Structures, which previously could be surmised by serial section transmission microscopy, can now be viewed directly. This technique was recently applied in the examination of the trabecular meshwork by Spencer[1] and Anderson.[2]

Classically,[3] the lens capsule is described as a clear membrane surrounding the lens, composed of a capsule proper or cuticular layer, and the zonular lamella, or superficial layer. The zonular fibers insert into the zonular lamella of the lens, each point of attachment producing a tent-like elevation of the lamella. No direct connections between zonular fibers and the cuticular layer is noted.

## MATERIALS AND METHODS

A total of four lenses were examined in this study, two samples being surgical specimens of cataract, and the other two, removed from bank globes, considered to be normal.

All material was fixed in 10% formalin for several days, then dehydrated in 70% alcohol for 24 hours and absolute alcohol for 30 minutes. The dissected specimen was attached to fragments of standard glass slides by vinyl adhesive and air-dried for six to 12 hours. Dehydration was completed by a vacuum evaporator, after which the specimens were coated with a thin layer (20 nm) of gold deposited at multiple angles. Appropriate grounding was accomplished by use of silver cement between the specimen and the microscope stage. Viewing was performed with a model JSN-2 scanning electron microscope (Japan Electron-Optics Laboratory).

## RESULTS

The anterior face of the lens consists of a moderately smooth surface marked by gentle undulations and a regular cobblestone-like mound pattern. These mounds are presumed to be the cells of the subcapsular epithelium. The mounds measure approximately 10μ in diameter. Spacing between the cobblestone mounds is small, generally no more than a micron or two. Prominence of the anterior epithelial cells in bold relief can be attributed to the dehydration process in preparation of the specimen. Areas of the posterior lens surface show a pitted surface structure. The crevices, measuring 0.5 to 1.5μ in size, are scattered in an irregular pattern, and may represent a type of capsular pore structure. Such openings were not noted on scanning the anterior lens surface.

Study of the equatorial region of the lens shows the zonular fibers attaching to the lens capsule. Larger fibers measuring 10μ or more subdivide into numerous smaller zonular fibers as the point of insertion is approached. The smallest fibers measure between 1 to 3μ and run a tangential course of nearly 0.5 mm semi-fused to the zonular lamella before the two structures blend imperceptibly together. Nearing the point of insertion, the fiber is adherant to the capsule by a mucoid-like substance which fills the gutter

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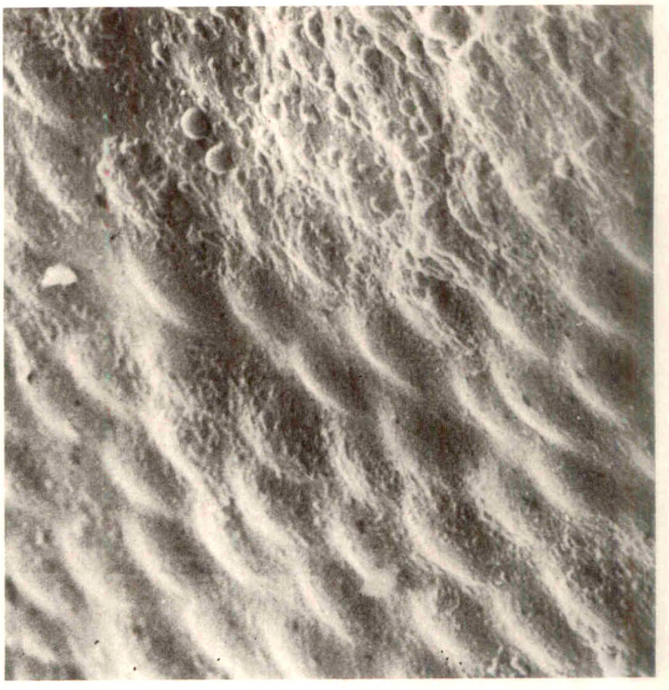


Fig. 1 (Oberman). Surgical specimen of senile cataract. The cells of the anterior subcapsular epithelium produces cobblestone-like mounds of the anterior capsule. (×1740).



Fig. 2 (Oberman). Normal eye bank globe. Numerous crevices representing the pore structure of the posterior lens surface. (×1740).

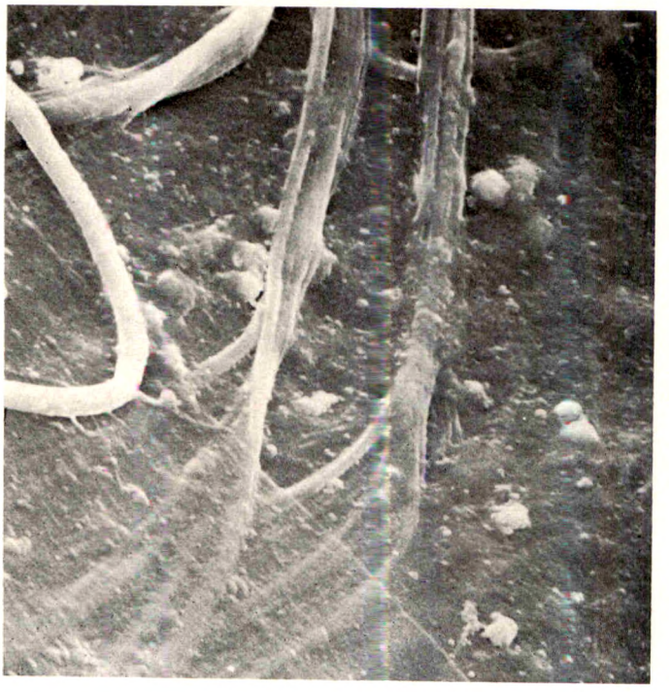


Fig. 3 (Oberman). Normal eye bank globe. Several zonular fibers at the equatorial region showing subdivision and insertion into the lens capsule. (×580).

between that fiber and the surface of the capsule. At the actual point of attachment of the fiber to the zonular lamella, the two appear to be interfused, both structures showing a common homogenous surface pattern.

## Comments

The microscopic anatomy of the lens surface and zonular attachments has been extensively described by techniques of conventional microscopy, phase-contrast microscopy,[4] and by transmission electron microscopy. The scanning electron microscope provides yet another means of examining the eye and its many surface features. Pictures obtained parallel the ophthalmologist's direct view of ocular structure by his standard office instruments.

Insertion of the zonular fibers into the zonular portion of the lens capsule is demonstrated with added realism by scanning electron microscopy. Division of the larger fibers into multiple smaller fibrils is well visualized, as is the long contiguous course of the fibril with the lens capsule prior to insertion. Visible morphology does not appear to differ from description of the insertions noted by other microscopic techniques.

Of particular interest was the demonstration of surface crevices. Capsular pores, as noted by Monahan,[5] have been postulated to serve as channels of diffusion into the lens substance. These channels, of 0.2 to 0.5μ size, were found to be less numerous with age and with degree of cataract. In contrast to this study, the channels were noted only on the anterior surface of the lens and were smaller in size.

Since it is known that the lens is metabolically active, consideration should be given to such crevices as being a route of entrance and exit of molecules through the capsule. Alteration of the pore structure may bear some relationship to the formation of posterior subcapsular cataract and the disturbed lens metabolism which is presumed to be present. These considerations deserve further study. Other investigators[6] feel the pores are artifacts in the fragile lens capsule, developing during removal and sectioning

and not observed with transmission electron microscopy. This possibility of artifact must always be considered in any process requiring severe dehydration of fragile tissues.

## Summary

The scanning electron microscope provides a study of the surface features of the lens and the zonular insertions. Because of the three-dimensional effect of this technique, views of zonular fiber insertion into the lens capsule are seen with improved realism. In addition, crevices representing a pore structure of the capsule are noted in several specimens. These openings may be related to the metabolic activity of the lens.

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### Ophthalmic miniature

. . . It is clear that it is the northern parts of Europe which are richest in gold, but how it is procured is another mystery. The story goes that the one-eyed Arimaspians steal it from the griffins who guard it; personally however I hesitate to believe in one-eyed men who in other respects are like the rest of us . . .

Herodotus
The Histories

# LOCALIZATION OF TRITIATED DIGOXIN IN THE RAT EYE

WILLIAM LISSNER, M.D., JAMES E. GREENLEE, M.D., J. DOUGLAS CAMERON, M.D., AND SEYMOUR B. GOREN, M.D.

*Chicago, Illinois*

The ocular symptoms of digitalis toxicity may include visual hallucinations, chromatopsia, blurred vision, pupillary changes, and decreased visual acuity. However, the mechanisms involved in the production of these ocular manifestations are not completely understood. Additionally, the biochemical interactions between the cardiac glycosides and the formation of aqueous humor are of interest. Sodium-potassium-ATPase, an enzyme active in transport systems, may be inhibited by the cardiac glycosides. Therefore, digitalis may be useful in the study of aqueous humor dynamics.

By means of tritium-labeled digoxin and autoradiographic and scintillographic techniques, the localization of digoxin in the rat eye was investigated.

## METHOD

Sprague-Dawley rats, each weighing approximately 350 mg, received a single intraperitoneal dose of 0.048 to 0.250 mg/kg of tritiated digoxin having a specific activity of 9 curies per millimole. At times varying from 15 to 180 minutes after injection, the animals were anesthetized with ether, the eyes and brain removed, and the tissues studied as described below.

*Autoradiographic studies*—After the eyes were enucleated and portions of brain excised, a freeze-dry technique was employed to eliminate leeching. The tissues were frozen immediately and stored in liquid nitrogen until sectioned. Sections 4 to 6 μ thick were cut with a cryostat under vacuum. The tissues were mounted on glass slides and covered with Kodak NTB-3 liquid emulsion, using the dipping technique. Following the exposure of the emulsion to the radioactivity, the emulsion was developed and the underlying tissue stained with hemotoxylin and eosin. Ten eyes were examined in this manner.

*Scintillographic studies*—Both eyes were enucleated and the cornea, iris, lens, retina, and sclera separated by microdissection. Multiple samples of proximal and distal optic nerve, occipital lobe, and cardiac blood were obtained. In some experiments, samples of aqueous and vitreous humor were removed prior to enucleation. Each tissue sample was placed in a Packard low-potassium glass counting vial and weighed.

The tissues were solubilized with 1.5 ml Soluene (Packard) and incubated for 20 hours at 40°C and 30% hydrogen peroxide was added to bleach the solution and to reduce color quenching. Glacial acetic acid was then added to acidify the solution and to minimize chemical luminescence. Scintillation solution (5 g PPO and 300 mg POPOP per liter of toluene) was added to each vial.

The samples were counted in a Packard Tri-Carb liquid scintillation counter. Quenching was compensated for by using internal standard techniques. The data was statistically analyzed using the Signed-Ranks test. Grouped data were used to compare the retina to other ocular tissues, to optic nerve, to brain, and to blood to determine if the differences in radioactivity were statistically significant.

## RESULTS

*Autoradiography*—Autoradiograms revealed extremely high concentrations of ra-

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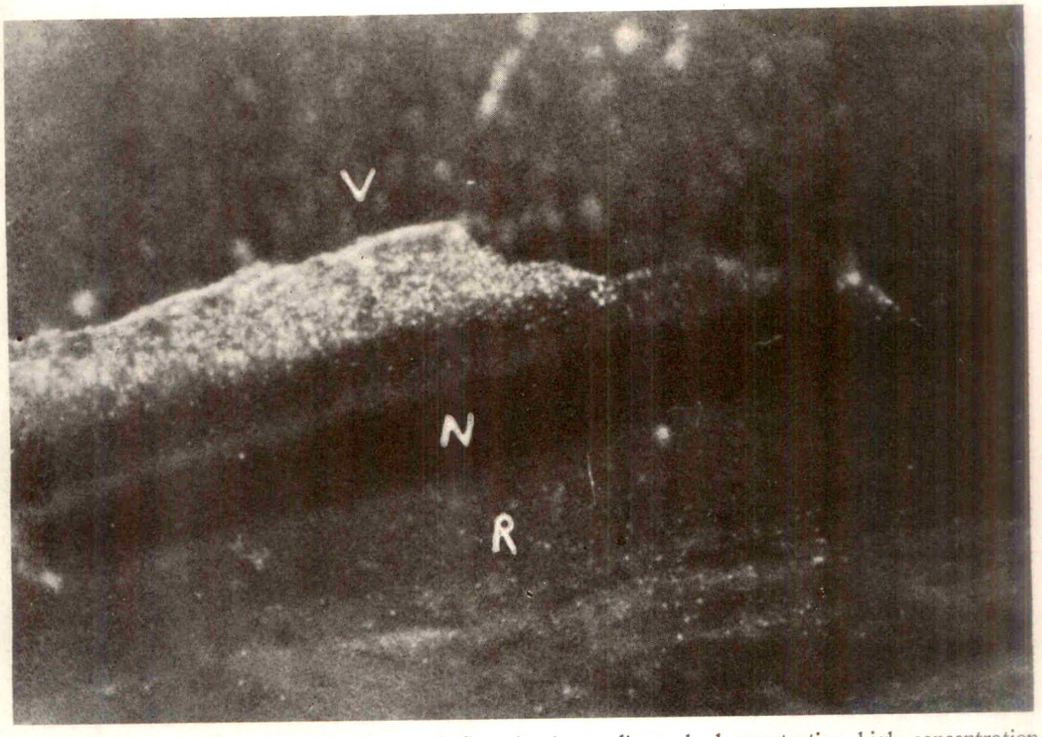



Fig. 1 (Lissner, Greenlee, Cameron, and Goren). Autoradiograph demonstrating high concentration of digitalis in the inner retinal layers and ganglion cells. The receptor cells (R), nuclear layer (N) and vitreous (V) contain minimal amounts of radioactivity.

dioactivity in the inner retinal layers, especially the ganglion cells (Fig. 1). Negligible amounts of digitalis were found in the outer retinal layers and receptor cells. Large amounts of radioactivity were spread diffusely throughout the iris (Fig. 2). Radioactivity was seen between the extraocular muscle bundles but not within the muscle fibers (Fig. 3). The conjunctiva contained moderate amounts of radioactivity (Fig. 4). The blurred quality of the photographs is due to the fact that the radioactive emulsion is being focused upon and not the underlying tissue. The cornea, lens, anterior and posterior chambers, vitreous, and sclera contained no radioactivity on the autoradiograms. Multiple sections of proximal and distal optic nerve and brain also revealed no radioactivity by autoradiographic techniques.

*Scintillography*—Using the scintillation counter, we found the retina and iris to have the highest concentration of digoxin. The sclera, cornea, lens, aqueous, and vitreous had progressively less. Most importantly, digoxin localized in the retina in concentrations 50 times that of the brain and 20 times that of the optic nerve (Table 1).

The Signed-Ranks test was used for statistical analysis of the data. Absorption of digitalis after intraperitoneal injection is variable and therefore it is not significant to compare absolute values in one animal with those of another. Additionally, different doses were administered in various experiments. However, the relative values between various tissues remained constant regardless of the time interval between injection and sacrifice or of the dosage given. Unfortunately, attempts at intravenous administration caused death in most animals. The Signed-Ranks test confirmed that the retinal concentration was significantly higher than brain, blood, and all other ocular tissues except the iris when P is 0.01 (Table 2).

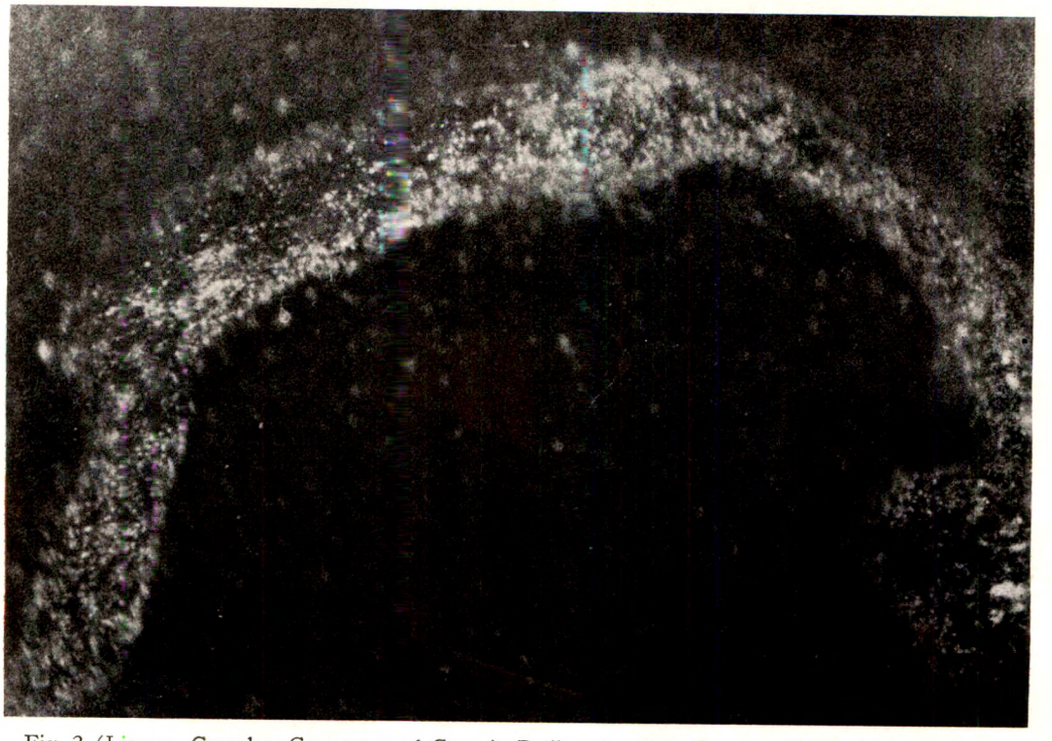


Fig. 2 (Lissner, Greenlee, Cameron, and Goren). Radioactive digitalis spread diffusely throughout the iris.

## Discussion

In his classic study of the medical uses of digitalis, Withering[1] stated that "foxglove, when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision with objects appearing green or yellow." The most common ocular symptoms of blurred vision and chromatopsia occur in 11[2] to 25%[3] of patients who develop digitalis toxicity. Less frequently, photophobia, scotomata, amblyopia, and even blindness may occur.[4]

The mechanisms by which these visual disturbances are produced are not clear. Wagener and his co-workers[5] felt that the cardiac glycosides caused a toxic effect directly upon the optic nerve. Sprague and associates[6] and Turtz[7] believed that the visual symptoms resulted from a toxic amblyopia.

Langdon and Mulberger[8] concluded that the visual disturbances arose from the cerebral cortex rather than from the optic nerve or retina. Changes in the cerebral cortex and spinal cord have been produced in cats with toxic doses of digitalis.[9]

Other investigators feel that the site of visual disturbances is the retina. Denden[10] found electroretinographic changes in a patient with visual symptoms secondary to digitalis toxicity. Gibson, Smith, and Alpern,[11] using electroretinograms, foveal photopic spectral sensitivity, and dark adaptation, concluded that digitalis acts directly upon the retina. These authors demonstrated a selective disturbance in the red-cone color system. Lufkin and his co-workers,[12] using tritiated digoxin, showed that the cat retina has a marked affinity for the drug.

Robertson, Hollenhorst, and Callahan[4] found abnormal receptor function in patients with digitalis toxicity. These same authors later found an elevation of dark adaptation in subjects maintained on non-toxic doses of long-term digitalis.[13] These elevated

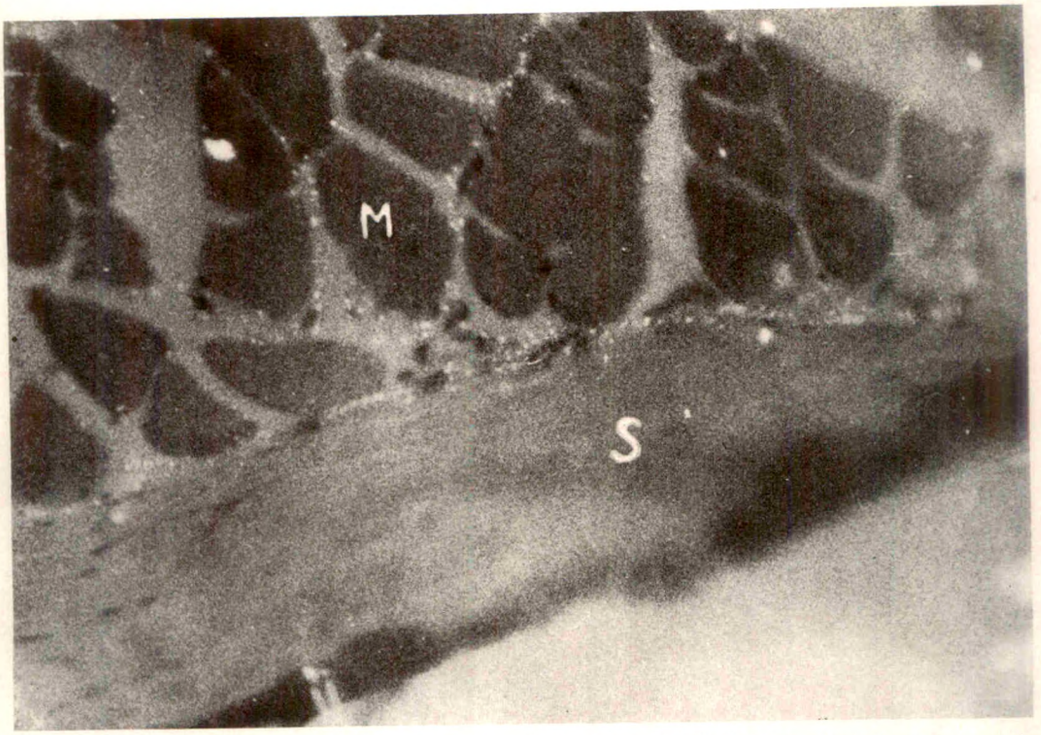



Fig. 3 (Lissner, Greenlee, Cameron, and Goren). Radioactive digitalis between the extraocular muscle bundles but not within the muscle fibers (M). The sclera (S) is free of radioactivity.

thresholds returned to normal after digitalis was discontinued. They felt that digitalis can disturb the receptor cell and interfere with the function of the visual cortex, ciliary body, and cornea.

In addition to the well-known clinical symptoms of digitalis toxicity, interest in the cardiac glycosides received great impetus when it was found that digoxin reduces aqueous humor inflow and intraocular pressure in man.[14] It was believed that digoxin exerts its effect by inhibiting the enzyme Na-K-ATPase in the ciliary body. Studies by Bonting, Simon, and Hawkins[15] revealed high concentration of Na-K-ATPase in the ciliary body in both cat and man. It was felt that Na-K-ATPase was a significant factor in aqueous humor production.[16] This enzyme is involved in active transport mechanisms. After a cell has been depolarized, Na-K-ATPase facilitates the pumping out of excess sodium ions from the cell and potassium ions back into the cell, thereby preparing the cell for further excitation.

Smith and Mickatavage[17] found that the topical application of various cardiac glycosides caused a slight decrease in intraocular pressure, but that these drugs caused a toxic keratopathy. Peczon[18] showed that systemically administered digitalis had only a small questionable effect on intraocular pressure in man. Although the cardiac glycosides have been found to be of little clinical value in the treatment of glaucoma, the research implications of these drugs in the study of aqueous humor dynamics are significant.[19]

By using both autoradiographic and scintillographic techniques in the present investigation, we are able to support the theory that digitalis causes its toxic effects by direct action upon the retina. However, unlike previous studies in which the receptor cell was considered to be the site of action, this work points to the inner layers of the retina, espe-

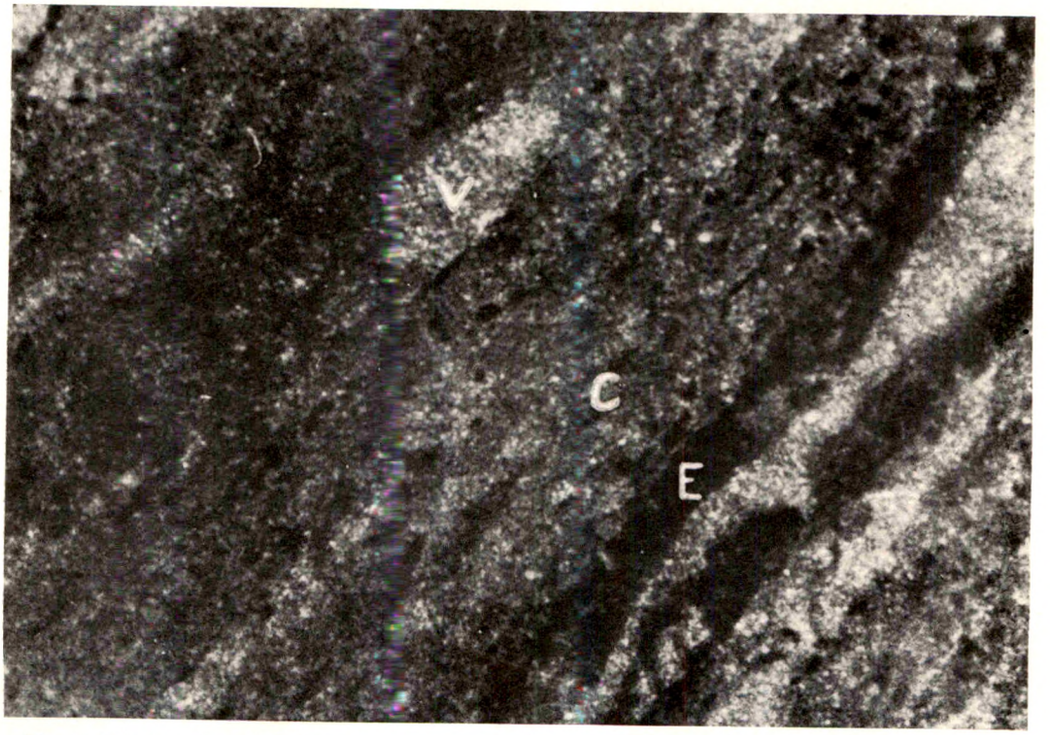



Fig. 4 (Lissner, Greenlee, Cameron, and Goren). Radioactivity throughout the conjunctiva. The epithelium (E), connective tissue (C) and vein (V) contain radioactive digitalis.

cially the ganglion cells, as the binding site of digitalis. It is true, however, that the localization of a drug in a cell does not necessarily imply that the drug acts on that specific cell. The concentration of a drug in a particular tissue is not necessarily related to its pharmacologic activity. Minimal amounts of digitalis were seen in the outer retinal layers and receptor cells. Autoradiographic studies done at varying time intervals after digitalis administration failed to demonstrate significant amounts of radioactivity in any area of the retina except the inner layers, especially the ganglion cells. While digitalis may diffuse throughout the retina, this study shows that the drug is rapidly bound to the ganglion cell. High concentrations of Na-K-ATPase have been found in the retina, especially in the rod fraction.[20] Possibly, digitalis acts by inhibiting the action of Na-K-ATPase in restoring the ionic gradients in the ganglion cell. However, an attempt to find Na-K-ATPase in the ganglion cell has not yet been successful. Further investigation is being conducted in this area.

Significant amounts of digoxin were also found in the iris. A definitive ciliary body was not found in the rat eye but iris processes were abundant. Radioactivity was found evenly dispersed throughout the iris processes and a specific cellular binding site could not be visualized autoradiographically. Lufkin and his associates[12] also found relatively high concentrations of tritiated digoxin in the ciliary body and iris of cats. These findings support the thesis that digoxin acts upon the secretory mechanisms by inhibiting Na-K-ATPase and thereby decreases aqueous inflow.

Using autoradiographic techniques, no digitalis was found in various sections of optic nerve, brain, sclera, lens, cornea, or ocular fluids. Although small quantities of digitalis were found in these tissues with scintillo-

TABLE 1

SUMMARY OF SCINTILLOGRAPHIC DATA ON 12 ANIMALS
(Showing disintegration per minute per mg)

| | Dose (in mg/kg) and Time (in hours) | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.104 2 | | 0.230 2 | | 0.048 2 | | 0.073 2 | | 0.110 2 | | 0.124 2 | | 0.151 2 | | 0.142 2 | | 0.147 1 | | 0.118 3 | | 0.119 1 | | 0.146 0.25 | |
| | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE | RE | LE |
| Vitreous | | | | | | | | | | 96 | | | 130 | 110 | 279 | 144 | | 2 | 167 | 62 | | 78 | 141 | 331 |
| Aqueous | | | | | | | | | 220 | 132 | 107 | 115 | 270 | 180 | 114 | 145 | 2148 | 12 | 121 | 79 | 61 | | 127 | 162 |
| Blood | | | 2460 | 2020 | 392 | 490 | 239 | | 1000 | 460 | 760 | 772 | 80 | 6640 | | 694 | 1419 | 2202 | 620 | 912 | 288 | 264 | 1492 | 1639 |
| Brain | 146 | 146 | 258 | 236 | 133 | 65 | 78 | | | | 167 | 184 | 190 | 220 | 144 | 138 | 178 | 187 | | 80 | 47 | 90 | 138 | 118 |
| Optic nerve | 207 | 207 | 547 | 334 | 60 | 61 | 210 | | | | 204 | 248 | 650 | 1710 | 344 | 306 | 399 | 328 | 479 | 205 | 136 | 100 | 432 | 1096 |
| Cornea | 184 | 147 | 463 | 407 | 145 | 177 | 211 | | | | | | 1050 | 2190 | 180 | 479 | 787 | 450 | 240 | 190 | 218 | 208 | 624 | 509 |
| Iris | 2130 | 1940 | | 4115 | | 715 | 2540 | | | | 5050 | 1670 | 23 | 446 | 855 | 4706 | 3107 | 3944 | 998 | 469 | 1175 | 1469 | 1595 | 3652 |
| Lens | 43 | 41 | 119 | 136 | 51 | 152 | 56 | | | | | | 70 | 80 | | | | | 59 | | | | | |
| Retina | 2048 | 865 | 2040 | 2720 | 995 | 695 | 522 | | 2360 | 1200 | 897 | 1060 | | 80090 | 4363 | 20768 | 2123 | 43057 | 639 | 1676 | 737 | 409 | 1845 | 1191 |
| Sclera | | | | | | | | | 591 | 673 | 845 | 973 | 2250 | 3540 | 727 | 105 | 2307 | 2027 | 275 | 1139 | 343 | 281 | 1344 | 1729 |

TABLE 2

ANALYSIS OF SCINTILLOGRAPHIC DATA

| | Mean DPM/mg* | No. Samples | % Retinal Concentration | Significant Difference from Retina† |
|---|---|---|---|---|
| Retina | 7831 | 22 | 100.0 | — |
| Iris | 2137 | 19 | 27.3 | No‡ |
| Blood | 1242 | 20 | 15.9 | Yes |
| Sclera | 1197 | 16 | 15.3 | Yes |
| Cornea | 466 | 19 | 5.9 | Yes |
| Optic nerve | 393 | 21 | 5.0 | Yes |
| Anterior aqueous | 266 | 15 | 3.4 | Yes |
| Occipital brain | 147 | 20 | 1.9 | Yes |
| Vitreous | 140 | 11 | 1.8 | Yes |
| Lens | 81 | 10 | 1.0 | Yes |

* DPM/mg = disintegration per minute per mg.

† P = 0.01.

‡ Iris not significantly different from retina at 0.01 or 0.05 level.

graphic techniques, this was probably due to contamination during the microdissection.

## SUMMARY

Localization of tritium-labeled digoxin in the eye of the rat was investigated, using autoradiographic and scintillographic techniques. The iris and inner retinal layers were found to be the primary binding sites of digitalis. Negligible amounts of radioactivity were found in the outer retinal layers, brain, and optic nerve.

## ACKNOWLEDGMENT

We thank Mrs. Cleoma Smith for her technical assistance.

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OPHTHALMIC MINIATURE

"Now, attend, Mr. Weller," said Serjeant Buzfuz, dipping a large pen into the inkstand before him for the purpose of frightening Sam with a show of taking down his answer. "You were in the passage, and yet saw nothing of what was going forward. Have you a pair of eyes, Mr. Weller?"

"Yes, I have a pair of eyes," replied Sam, "and that's just it. If they wos a pair o' patent double million magnifyin' gas microscopes of hextra power, p'raps I might be able to see through a flight o'stairs and a deal door; but bein' only eyes, you see, my wision's limited."

Charles Dickens
*The Pickwick Papers*, 1836-7

# METHOD OF CORRECTION OF TARSAL ECTROPION

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The term tarsal ectropion is used by Fox[1] to describe lower eyelid eversion that is limited to the tarsal-containing portion only. It has sometimes been described as spastic ectropion, a term which, according to Duke-Elder,[2] erroneously relates its development to spasm of the marginal fibers of the orbicularis muscle and which should be reserved for those cases of ectropion occurring in young people and characterized by a facile reduction. Tarsal ectropion (Fig. 1) cannot be reinverted by manual reduction.

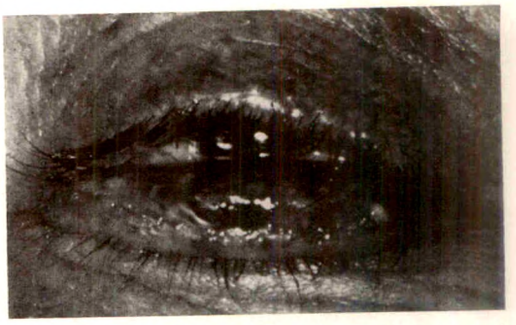


Fig. 1 (White). Preoperative appearance of tarsal ectropion.

In tarsal ectropion, Fox further observes that there is no relaxation of the tissues of the eyelid below the tarsus as in senile ectropion. Further, an actual shortage of skin appears to develop (Fig. 2). The following technique uses the skin to reinvert the tarsus.

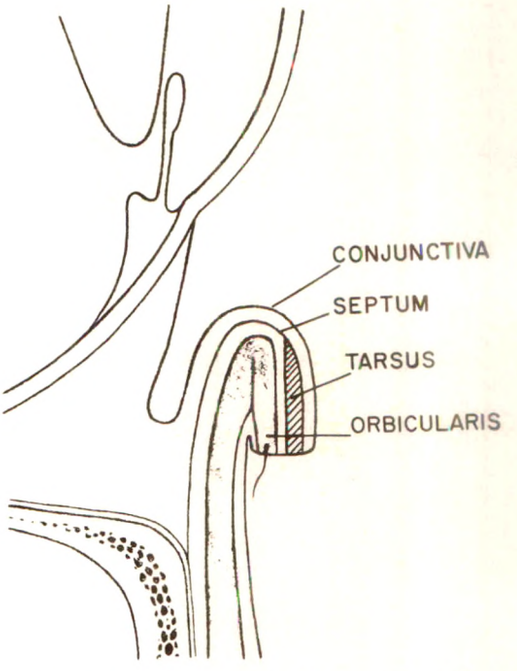



Fig. 2 (White). Diagramatic cross-section of tarsal ectropion.

## TECHNIQUE

Two traction sutures are first placed through the margin of the lower eyelid and traction is exerted in an upward direction. A horizontal incision is then made through the skin about 4 mm below and parallel to the margin of the lower eyelid, preferably in the line of a skin fold. The incision should extend over the middle two-fourths of the eyelid. The skin above and below the incision is carefully freed from the underlying orbicularis muscle (Fig. 3). It is important that adequate mobilization of the skin below the incision be obtained. Dissection is then carried upward between the folded layers of the orbicularis until the inferior border of the tarsus is reached (Fig. 4). The orbicularis is incised at this point and the inferior border of the tarsus is exposed for its entire length (Fig. 5). Three double-armed sutures of 5-0 silk are inserted horizontally in the inferior border of the tarsus, one in the midline and one to each side. The sutures are then brought out through the skin below the incision line. The distance

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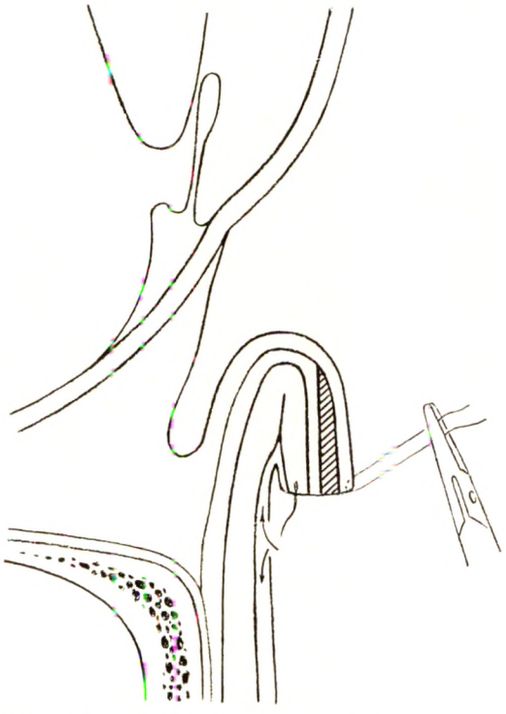


Fig. 3 (White). Skin freed from orbicularis muscle.

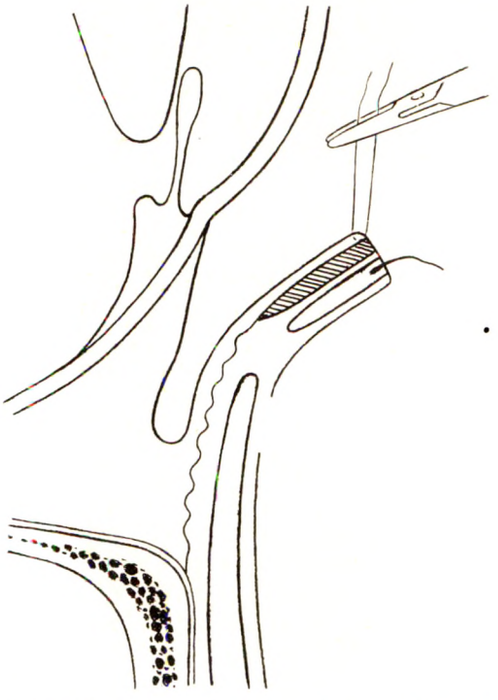


Fig. 5 (White). Lower border of tarsus dissected free.

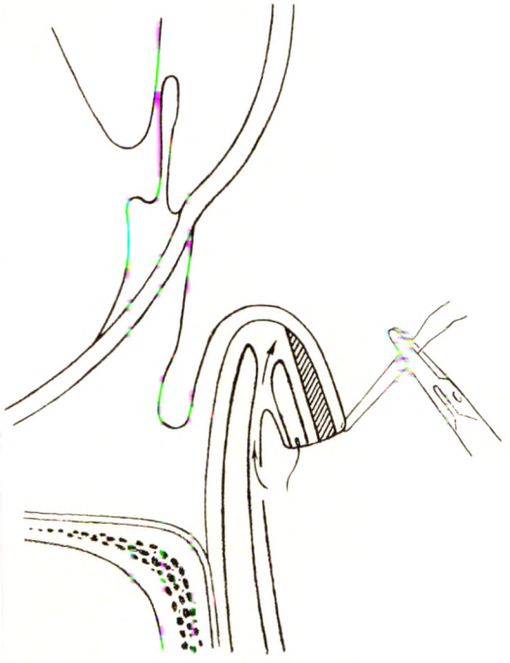


Fig. 4 (White). Incision of orbicularis to reach lower border of tarsus.

of the suture from the incision is usually about 2 mm, but this distance may be varied according to the need for inversion. Overcorrection, with consequent dragging down of the lower eyelid margin, should be avoided. Each suture is passed through a peg of rubber tubing and pulled tight (Fig. 6). Overcorrection and undercorrection can be adjusted, if necessary, by replacement of the sutures. Finally, the sutures are tied over the rubber pegs. They should be left in place for approximately 10 days. The skin incision is closed with interrupted silk sutures which may be removed after five days. The postoperative appearance after removal of all sutures is shown in Figure 7.

The result of this procedure is that the lower border of the tarsus becomes firmly attached through the opening in the orbicularis to the skin beneath the incision, thus correcting the ectropion.

Eight such procedures have now been performed, with satisfactory reinversion of the

tarsus in all. In one case residual horizontal eyelid laxity required bilateral correction by the Kuhnt-Szymanowski procedure. In another case residual eyelid laxity was corrected at the time of the original surgery by a modified Szymanowski procedure. This was achieved by extending the horizontal skin incision 2 cm in an upward and lateral direction and then making a downward vertical incision in the usual manner.

## Discussion

Procedures such as the Kuhnt-Szymanowski operation which exert their effect by horizontal shortening of the eyelid do not correct advanced cases of tarsal ectropion where the defect is in a vertical direction. They may even make the ectropion worse by fixing the tarsus more tightly in its everted position.

Shortening of the orbital septum would appear to be one logical approach to the problem. Jones and associates[3] describe a method of tucking the orbital septum for the correction of senile entropion. In one case of tarsal ectropion, satisfactory inversion was obtained by this method, but the lower eyelid was drawn down well below the normal position. This result appears to be the result of failure to resolve the problem of lack of skin in the lower eyelid.

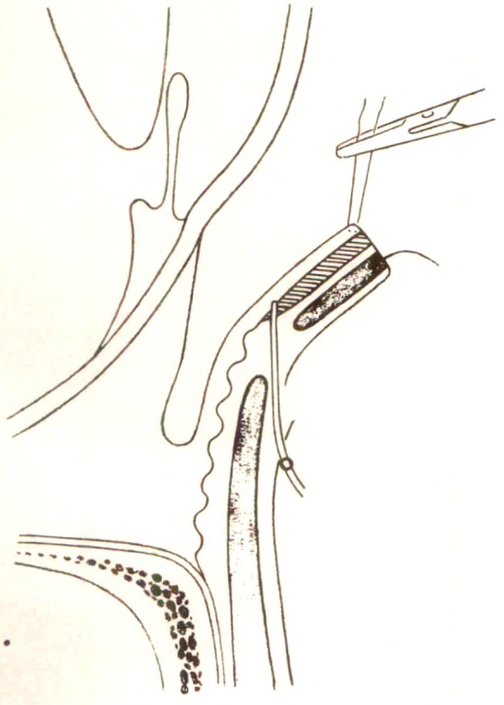


Fig. 6 (White). Insertion of sutures through tarsus and skin.

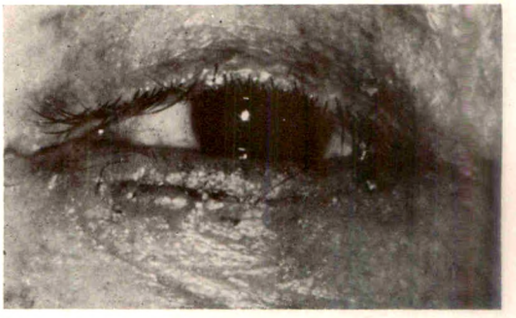


Fig. 7 (White). Postoperative appearance 10 days after surgery.

The technique described earlier is an extension of the Snellen suture technique.[4] It transfers the pull of the skin from the upper margin of the tarsus to the anterior lower border. This reinverts the tarsus around its horizontal axis through the medial and lateral palpebral tendons. Any further downward pull of the skin holds the tarsus in its vertical position.

## Summary

To correct tarsal ectropion, the lower edge of the tarsus is exposed through a horizontal skin incision. This edge is sutured to the skin below the incision. Subsequent downward pull of the skin reinverts the tarsus.

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# GOLDENHAR'S SYNDROME AND PHOCOMELIA

## Case Report and Etiologic Considerations

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Goldenhar's syndrome,[1] in which epibulbar dermoids are associated with ear abnormalities, is one of four syndromes in which congenital malformations that involve the eye result from an abnormal development of the first, or first and second, branchial arches.[2] The others are Franceschetti-Klein (Treacher Collins), and the Pierre Robin, and Hallerman-Streiff syndromes. Although sometimes showing a few manifestations seen in Franceschetti-Klein's syndrome, which is a dominantly inherited condition, Goldenhar's syndrome is an entirely distinct clinical entity.[3-9] In all cases Goldenhar's syndrome is sporadic and nonfamilial; its etiology is unknown.

This paper describes the occurrence of phocomelia in a patient with Goldenhar's syndrome, an association not previously reported. The features of this case are presented in detail in an attempt to throw some light on the etiology of the syndrome.

### Case report

The patient, a boy, was first admitted to the Hospital for Sick Children, Toronto, at the age of two and one-half years for investigation of skeletal malformations and recurrent vomiting. His mother, was 21 years old at the time of his birth. In the seventh week of gestation, unaware that she was pregnant, the mother had developed abdominal pains, nausea, and vomiting for which she had taken three pills thought to be Midol (acetyl salicylic acid, phenacetin, caffeine, and cinnamylephedrine). A few days later she was treated for a threatened abortion, but the pregnancy continued. In the 10th week she had an appendectomy. The operation was without complication, and the rest of the pregnancy was uneventful; the patient was born at term and delivery was normal.

On admission the child was alert and intelligent, of average height and weight for his age. His right arm consisted of a hypoplastic humerus, short ulna, three metacarpals, and two fingers. His left arm consisted of a normal humerus, short ulna, four metacarpals, and four fingers (Fig. 1). On the right side of the face he had a preauricular skin tag, atretic external ear canal, and poorly formed pinna (Fig. 2). He had a grade I presystolic murmur at the left sternal border.

Eye examination revealed a fleshy, yellowish tumor of the bulbar conjunctiva of the right eye and a coloboma of the right upper eyelid.

The chromosome pattern was normal male (46XY) and routine laboratory tests on blood and urine gave normal results. Spinal roentgenograms showed a spina bifida; an intravenous pyelogram demonstrated hypoplasia of the left kidney and a normal right kidney; and an upper gastrointestinal series revealed partial obstruction of the third stage of the duodenum. Exploratory laparotomy showed a partially annular pancreas, incomplete rotation of the cecum, and a partial duodenal stenosis. In order to relieve the partial obstruction of the small bowel, a duodeno-duodenostomy was performed.

Surgical treatment of the eye lesions was postponed because of the surgery on the small bowel.

At the age of five years the boy was readmitted for treatment of his eye problems. His general clinical condition was unchanged. His visual acuity was 20/30 in the right eye (refractive error +1.50 sph. ⊃ +3.50 cyl. ax. 110) and 20/20 in the left (refractive error +1.00). The corneal diameters were 10.0 mm in the right eye and 10.5 mm in the left. A fleshy, yellowish, noncystic mass involved the lower half of the temporal bulbar conjunctiva of the right eye and barely encroached on the limbus (Fig. 3). The coloboma of the right upper eyelid was unchanged (Fig. 4), and further examination revealed no other ocular abnormality. At operation the conjunctival tumor was totally excised.

### Discussion

The patient described in the original article by Goldenhar[1] had epibulbar dermoids, accessory auricular appendages, and a congenital auricular fistula, anomalies resulting from faulty development of the first and second branchial arches and the first branchial cleft. Other manifestations of the syndrome include coloboma of the upper eyelid, anti-

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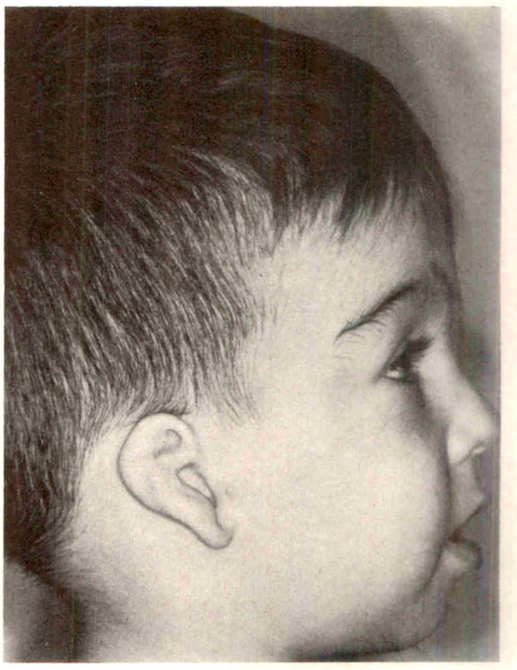


Fig. 2 (Mandelcorn, Merin, and Cardarelli). The patient at two and one-half years of age. Note the malformed right auricle and the preauricular skin tag.

mongoloid slant of the palpebral fissures, microphthalmos, microcornea, coloboma of the uvea, hypoplastic upper and lower jaw, microtia, and macrostomia.[10] In the 50 or so reported cases of Goldenhar's syndrome, however, several malformations are also described that involve structures other than those derived from the branchial arches. Anomalies of the cervical vertebrae, for example, are so common that Goldenhar's syndrome is often called the oculo-auriculo-vertebral dysplasia.[3,11] Other systemic, skeletal, neurologic and cardiovascular anomalies occur, including Duane's syndrome,[12] heart disease,[11,13] cleft palate,[11] mental retardation,[11,14] hydrocephalus, meningoencephalocele,[15] and B-group chromosomal disorder.[14]

The broad nature of the syndrome is espe-

Fig. 1 (Mandelcorn, Merin, and Cardarelli). The patient at two and one-half years of age. Note the abnormalities of the upper limbs.

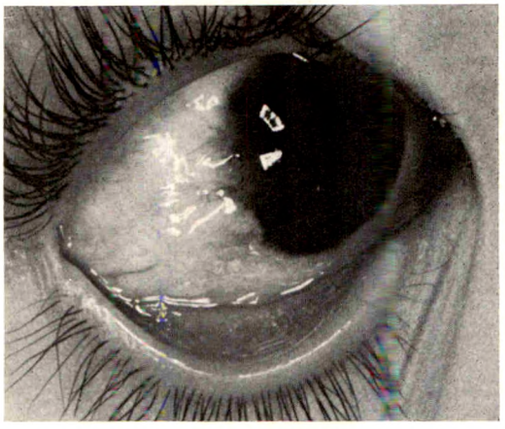


Fig. 3 (Mandelcorn, Merin, and Cardarelli). The right eye of the patient at five years of age, showing an epibulbar dermoid.

cially well illustrated in the present case, where the patient not only had the typical eye and ear anomalies leading to the diagnosis of Goldenhar's syndrome, but also had phocomelia, renal hypoplasia, a partially annular pancreas, incomplete rotation of the cecum, and duodenal stenosis. These findings emphasize that in the management of every case of Goldenhar's syndrome one must suspect and search for the presence of other systemic malformations.

Broadening the view of Goldenhar's syndrome to admit the generalized malformations is important with regard to the etiology. To date, those authors who consider Goldenhar's syndrome solely as a branchial arch malformation have come to no definite conclusions about etiology. Only three authors have suggested possible causes, despite the many cases reported. Smithells[13] reported a case of Goldenhar's syndrome in which the patient's mother had developed influenza in the sixth week of gestation. Ladekarl[14] reported on the occurrence of Goldenhar's syndrome in a patient whose mother had had a cholecystogram in the fourth week of gestation. In the case reported by Zweymüller and Stur,[16] the patient's mother had had rubella in the eighth week of pregnancy. Our case leads to the hypothesis that the etiologic agent was active during the seventh week of gestation—that is, when the patient's mother suffered from the abdominal pains and the threatened abortion and also ingested the three pills. This hypothesis of an external agent acting on the embryo during the seventh week of gestation can easily account for all the malformations seen in our patient—the ocular and external ear defects, the phocomelia, the renal atrophy, and the duodenal stenosis—because the development of all the affected structures normally occurs in the embryo at the same time, the seventh week. The branchial arches involved in Goldenhar's syndrome appear in the sixth week of gestation, but disappear by the eighth week when their derivatives, such as the ear, face, and eyelids, have differentiated. Similarly, in the sixth week, when the intestinal loop enters into the umbilical cord, the duodenal epithelium proliferates to occlude the lumen until the eighth week, when vacuolation restores a continuous lumen. By the seventh week, also, the metanephros has formed and the upper arm, forearm, and hand have separated from the trunk.[17] Clearly, one agent acting during the seventh week could easily have caused all the malformations seen in the present case.



Fig. 4 (Mandelcorn, Merin, and Cardarelli). The right eye of the patient at five years of age, showing a notching of the right upper eyelid.

The main skeletal abnormality in our patient was phocomelia, a malformation typically seen in "thalidomide babies." Even though those cases of phocomelia described before the thalidomide period were never associated with ocular abnormalities,[18] we cannot neglect the possibility that in the present case thalidomide was the cause of the phocomelia and the Goldenhar's syndrome. The case history, however, did not record any ingestion of thalidomide; and, although thalidomide does produce ocular abnormalities, Goldenhar's syndrome has never been described in thalidomide-damaged children.

We believe that in this case Goldenhar's syndrome was caused by a noxious agent active during the seventh week of gestation. What this teratogenic factor was, we cannot be sure. It might have been the same agent that caused the threatened abortion. It might have been the drug which the mother ingested, whether this was a mixture of acetyl salicylic acid, phenacetin, caffeine, and cinnamylephedrine as claimed, or thalidomide, as might be suspected from the phocomelia. It might have been a virus as suspected in Smithells'[13] and Zweymüller and Stur's[16] cases. Whatever the agent might have been, our findings imply that it acted on the embryo during the seventh week of development.

## Summary

Goldenhar's syndrome, associated with phocomelia and intestinal and renal malformations, was seen in a two and one half year old boy. In the seventh week of gestation the mother had ingested an analgesic drug for abdominal pains, and this was followed by a threatened abortion. The concept is advanced that Goldenhar's syndrome consists of a group of generalized rather than localized malformations, and it is suggested that Goldenhar's syndrome is caused by an external teratogenic agent acting in the seventh week of embryogenesis.

### Acknowledgment

We thank Professor J. S. Crawford for reviewing this manuscript.

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# A TECHNIQUE FOR VISUAL APPRAISAL OF MENTALLY RETARDED CHILDREN

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Because of their intellectual handicap, it is of utmost importance that visual deficiencies of retarded children be recognized and corrected to provide maximum potential for learning. Unfortunately, many of these children have never had a visual examination; further, if one is performed, reliable data may be difficult to obtain. The child may be difficult to deal with, and frequently the ophthalmologist does not have a satisfactory method of examination in this situation. In working with a group of children with mental handicaps, we developed a practical system for their visual evaluation which we have described in this paper.

TABLE 1

CAUSES OF MENTAL RETARDATION

| | |
|---|---|
| Down's syndrome | 33 |
| Unknown | 29 |
| Brain damage | 13 |
| Non-verbal 9 | |
| Verbal 4 | |
| Cerebral palsy | 11 |
| Cerebral dysgenesis | 3 |
| Postencephalitis | 4 |
| Rh factor | 3 |
| Cerebral ataxia | 3 |
| Cranial dysostosis | 2 |
| Microcephalos | 1 |
| "Battered child" syndrome | 1 |
| Total | 103 |

## METHODS

A group of 103 day students was examined from the Orchard School for mentally handicapped children in Skokie, Illinois. These students, whose mental retardation resulted from various causes (Table 1), ranged in age from three to 22 years; each child's intelligence quotient was 60 or less. The school nurse devised a routine for familiarizing the students with the general procedure to be used in the examination. This resulted in a definite reduction of apprehension and permitted the children to be more cooperative, thus allowing a more thorough and accurate appraisal. The tests were performed in the Eye Clinic of Evanston Hospital at a time when other activities were not scheduled in order to provide a quieter and less disturbing environment. Each child was examined alone, with the nurse from the school in attendance for identification and reassurance. Because these children generally have a short attention span and are easily distracted, the test procedures were performed rapidly. When a test proved beyond the comprehension of a child, it was eliminated and the next procedure presented.

The initial approach was a general appraisal of the eyes and adnexa. Visual acuity was then recorded. Lippmann[1] has stated that young children do not have the concept of direction and therefore the illiterate "E" is usually unreliable. He also reported that these children require identification of one symbol at a time. These statements were confirmed in our study. "Pictographs" utilizing symbols familiar to children, as devised by Allen,[2] were attempted, but these children were unable to recognize these symbols and so another method was developed. We attempted the use of the Stycar test,[3,4] which employs cut-out symbols placed on a table to be matched with similar objects at a distance. This system did not prove successful because children with mental retardation frequently do not comprehend the concept of "likeness" or similarity.

Since most of the children could recognize food items (and often no others), selected items from the Peabody series[5] were photo-

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graphed in color to provide a series of 2×2 slides to be used with a projector. Because of the resolution of the projected picture, smaller symbols could not be satisfactorily reproduced. We therefore designed a wall chart printed in color using the food items, (apple, banana, "hot dog," and ice cream cone) calibrated for the standard 20-foot distance.* Each symbol can be framed by an adjustable framer to stimulate attention. This method proved successful in a high percentage of cases. (Fig. 1)

* The chart used in this study may be ordered as "Apple Chart" from Medical Contact Lens Service, 1225 Circle Tower, Indianapolis, Indiana 46204.

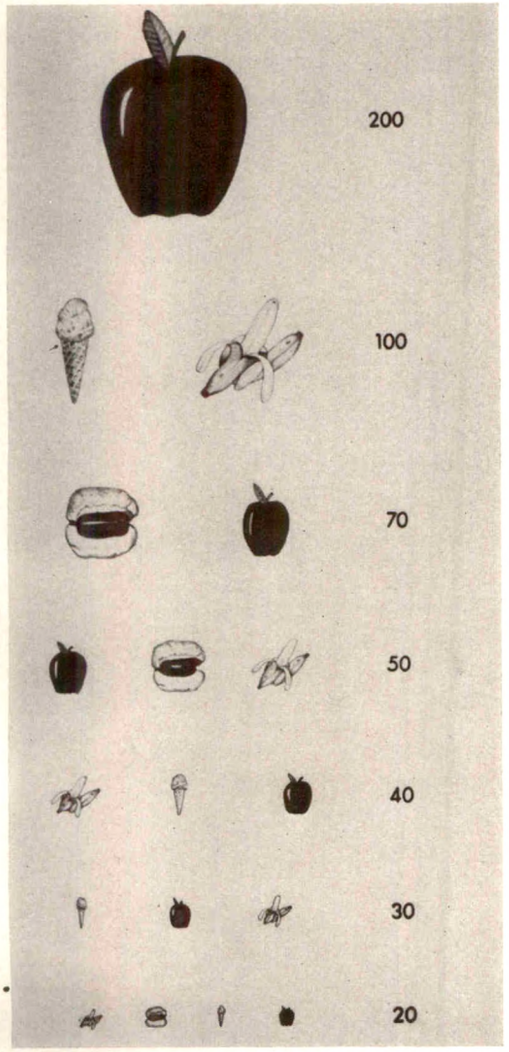



Fig. 1 (Lawson and Schoofs). Wall chart, printed in color and calibrated for the standard 20-foot distance, devised to test mentally retarded children.

TABLE 2

METHODS OF DETERMINING VISION

| Technique | No. Children |
|---|---|
| Snellen | 27 |
| "E" game | 14 |
| Food pictures | 36 |
| Could not test | 26 |

Ocular muscle coordination and the fusion status were then ascertained when possible, utilizing the Worth 4-dot, the Maddox rod and the Wirt Stereotest. Prism cover tests were also used. All of the children had retinoscopy performed under cyclopegia. The use of the refractor or trial frame was generally too frightening to the child. Therefore, either the loose lenses or the Foster retinoscopy rack was used; these methods were preferred because of their rapidity, and a fairly accurate measurement was possible in the majority of cases. The ocular fundi were examined for defects by indirect ophthalmoscopy, which proved to be vastly superior to the direct method because it enabled us to perform the examination without touching the child.

## RESULTS

With the system described above, we were able to determine the visual acuity of a significant number of this group of mentally retarded children. (Table 2) Unfortunately, there remain some children for whom no system yet devised is satisfactory. In our series there were 18 children who initially had less than 20/70 uncorrected vision in their better eye (sight-saving cut-off level), 15 of whom could be corrected to better acuity. These children had not previously been identified as having visual problems. Only 28% of our children were considered to be ophthalmologically normal, whereas in a general school population approximately 75% are usually found to be without visual motor or sensory difficulties.

A total of 44 children had significant re-

TABLE 3

TYPES OF REFRACTIVE ERRORS

| Condition | No. Eyes |
|---|---|
| Hyperopia | |
| 1.00–2.00 diopters | 6 |
| 2.25–4.75 diopters | 24 |
| Over 5 diopters | 9 |
| Myopia | |
| 1.00–2.00 diopters | 6 |
| 2.25–4.75 diopters | 6 |
| Over 5 diopters | 5 |
| Astigmatism | |
| 1.00–2.00 diopters | 9 |
| 2.25–4.75 diopters | 21 |
| Over 5 diopters | 2 |
| Total | 88 |

fractive errors (Table 3). In 25 of these the visual defects were unknown to the school or to the parents, and required corrective lenses. There were 19 children who were already wearing glasses, nine of whom needed significant changes in the power of their spectacles.

There were 33 of the 103 children who had some degree of ocular muscle imbalance (Table 4). This incidence is almost 10 times that of a normal population of this age group. There were nine students with an amblyopic eye who had never received treatment, and the majority of the parents had no previous knowledge of the condition. There were 18 with definite esotropia and four with significant esophoria. Six children had a constant exotropia, and four had an intermittent exotropia. Two children had had previous eye surgery.

## CONCLUSIONS

The results of our study demonstrate the need for an ophthalmic appraisal of the mentally retarded child. These children have a high incidence of visual defects which may influence their level of functioning, especially in a learning situation. The need for treatment of a visual defect must be individually determined and the school alerted to the special problems and visual needs of the child.

## SUMMARY

A group of 103 mentally retarded children varying in age from three to 22 years were examined for visual difficulties. Because of the inability to determine the visual acuity in many of these children by any available technique, a chart was designed utilizing food items printed in color and calibrated for the standard 20-foot distance. By this method, a substantial number of children can be added to those in whom the visual acuity can be determined. Only 28% of our children were considered ophthalmologically normal as contrasted to the approximately 75% in a normal school population. Among other ocular findings, 44 had significant refractive errors, 33 children were found to have ocular muscle imbalance, and there were nine students with an amblyopic eye.

## ACKNOWLEDGMENTS

We thank Julia S. Molloy, Director of the Molloy Education Center, and Mrs. Peg Miller, R.N., for their invaluable assistance in this project.

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TABLE 4

MISCELLANEOUS VISUAL FINDINGS

| | |
|---|---|
| Nystagmus | 10 |
| Partial blepharoptosis | 2 |
| Marginal blepharitis | 20 |
| Microphthalmos | 1 |
| Iris atrophy | 1 |
| Brushfield spots of iris | 18 |
| Corectopia | 1 |
| Zonular cataract | 1 |
| Posterior lenticonus | 1 |
| Cataracts | 2 |
| Retinopathy | 1 |
| Medullated nerve fibers | 1 |
| Optic atrophy | 1 |
| Hemianopsia | 1 |

# BLEPHAROPTOSIS, BLEPHAROPHIMOSIS, EPICANTHUS INVERSUS, AND TELECANTHUS—A SYNDROME WITH NO NAME

ROGER KOHN, B.A., AND PAUL E. ROMANO, M.D.
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Over the past 50 years, there have been numerous reports[1-32] of the triad of blepharoptosis, blepharophimosis, and epicanthus inversus. The consistency of the triad and its hereditary background make it a true clinical syndrome, and yet it has escaped both collation and appellation over the years.

This paper presents a collection and comparison of all cases previously reported. We think these illustrate that a fourth finding, telecanthus, is so consistent that it should be added to the triad. A family with this syndrome and several associated features not previously described is also reported.

In 1921, Komoto[4] described the first case with the triad, a patient who had, in addition, wide set eyes, ectropion, excessive brow hair, and hypoplasia of the caruncle and plica semilunaris. Three unspecified relatives of this patient were reported to have the same disorder.

Later that same year, Dimitry[6] reported a family with "blepharophimosis." He did not specify other findings, but from the photographs accompanying his report, it appears that this family had the complete triad. Dimitry did, however, trace the pedigree of the "blepharophimosis," which is the first and longest (after revision by Owens in 1960) pedigree of this syndrome (Fig. 1). In this pedigree, the syndrome appears in both sexes and is transmitted as a Mendelian dominant characteristic. This mode of inheritance is now well documented.

Since these early descriptions, 125 additional cases were reported. Of these, 12 were male, six were female, and in 107, sex was unspecified. A familial association appeared in 37, while two were definitely nonfamilial; in the remaining 86 cases, the possibility of familial association was not specified.

The three primary features of this syndrome are reported or evident in all cases. These findings tend to accentuate one another—their total effect is to constrict the palpebral fissure by reducing it in both height and width.

Numerous other findings are reported which are either compensatory responses or coexistent deformities. The levator palpebrae superioris is markedly hypoactive and fibrotic.[8,9] There is also a hypoplasia of the tarsal plates of the upper eyelids.[8,10,12] To compensate for the blepharoptosis, these patients assume a characteristic posture with the head tilted backward and the chin arched upward. The eyelids are covered by remarkably smooth skin without eyelid folds.[13,21] Several authors found deficient amounts of skin in both eyelids at surgery.[14,15] Vertically increased eyebrow width has been observed [12,14,15] and is attributed to a stretching of hair-bearing skin with constant contraction of the frontalis muscle. There are two changes associated with the epicanthus inversus—an increased length of the medial canthal ligament[10,16,17,30] and a lack of the normal depression seen at the internal canthus.[12,18] The caruncle and plica semilunaris are secluded to varying degrees beneath the epicanthal fold and usually have a hypoplastic appearance.

Abnormalities of the eyelid margin are frequently seen. The upper margin is characteristically S-shaped,[12,16,30] while the lower margin has a concavity downward, particularly in the lateral aspect, with or without slight ectropion.[4,12,16,17,30] Two authors found an inequality in the lengths of the upper and lower eyelids when measured at

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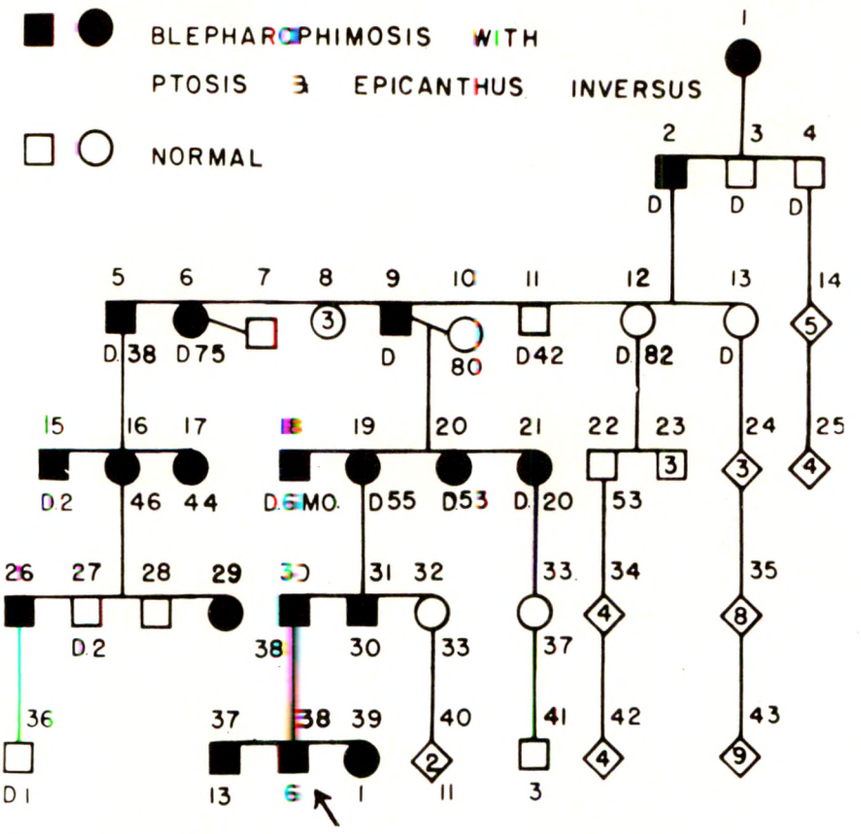



Fig. 1 (Kohn and Romano). Dimitry's original pedigree after revision by Owens.[12]

their margins.[7,10] Trichiasis was present on several occasions.[9,11]

The lacrimal system is often affected. Numerous reports describe a lateral displacement of the lower punctum, and two authors also describe a medial displacement of the upper punctum.[13,17] Other variations such as stenosis of all canaliculi,[17] elongation of the horizontal canaliculi,[7,10] and punctal reduplication[7,17] are noted.

Microphthalmos is described by one author,[19] and there are two reports of divergent strabismus and nystagmus.[26,31] As in simple blepharoptosis, underaction of the superior rectus and limitation of upward gaze are often found in this syndrome. No other muscle deficits are reported, with the exception of the inferior rectus—represented by limitation of downgaze.[20] Visual disturbances and amblyopia are considered uncommon.[10,30]

Several deformities of the facial bones are often seen in association with this syndrome. Many authors describe the root of the nose as being flat and broad, while one author also note a boney deficiency in the supraorbital rim and brow.[14] There are two isolated reports of a high arched palate.[11,12] Additionally, one study recorded 10 cases with "lop ears" (i.e., ears with an overhanging helix).

In contrast to their somewhat obtunded appearance, the mental status of individuals with this syndrome is usually normal, but some develop secondary psychological problems as a result of their cosmetic handicap.[18,15]

The hereditary pattern of this entity is well documented.[4-6,8,10-13,21,26,31] It is nor-

mally transmitted as an autosomal dominant with essentially 100% penetrance. Although seen in both sexes, it occurs more commonly in the male and is expressed more commonly through the male. Pedigrees have been recorded in eight families. All chromosome studies have been negative and a metabolic anomaly has not been discovered.

The surgical management of this condition is well covered in the current literature, and is beyond the scope of this paper.[7,9,10,16,18,22,25,35] Surgery should be undertaken early enough to prevent deprivation amblyopia, a possible sequela of severe blepharoptosis.

Throughout the literature the syndrome is constantly described as a triad consisting of blepharoptosis, blepharophimosis, and epicanthus inversus. We feel it should be considered a tetrad since telecanthus is also invariably present.

The term, telecanthus, was originated and defined by Mustardé[7,25] as an increased distance between the internal canthi. In primary telecanthus, this increase is clinically apparent, but there is no true hypertelorism (i.e., no radiologic evidence of increased distance between the orbits). Secondary telecanthus is an increased distance in the presence of true hypertelorism.

In virtually every case report reviewed, the triad was reported in association with either "increased intercanthal distance," "hypertelorism," "pseudohypertelorism," "increased distance between the eyes," or else such an increase in distance between the eyes was apparent from photographs. Since telecanthus is always present in hypertelorism (according to Mustardé[7]) and is synonymous with increased intercanthal distance, telecanthus may be said to have been present in all cases and the syndrome should be defined as a tetrad including it.

## Case reports

A family demonstrating this syndrome was recently seen at Children's Memorial Hospital Eye Clinic of Northwestern University. We examined three of these children, brothers, and obtained the pedigree from their unaffected mother. Our pedigree (Fig. 2), comprising four generations, consists of 30 individuals (19 males and 11 females). Sixteen of the 30 are affected (12 males and 4 females), closely approaching the classical 50% ratio of an autosomal dominant characteristic.

*Case* 1—This eight-year-old white boy (Figs. 3-5) was noted to have "small eyes" at birth. His condition is unchanged, but the family has consis-

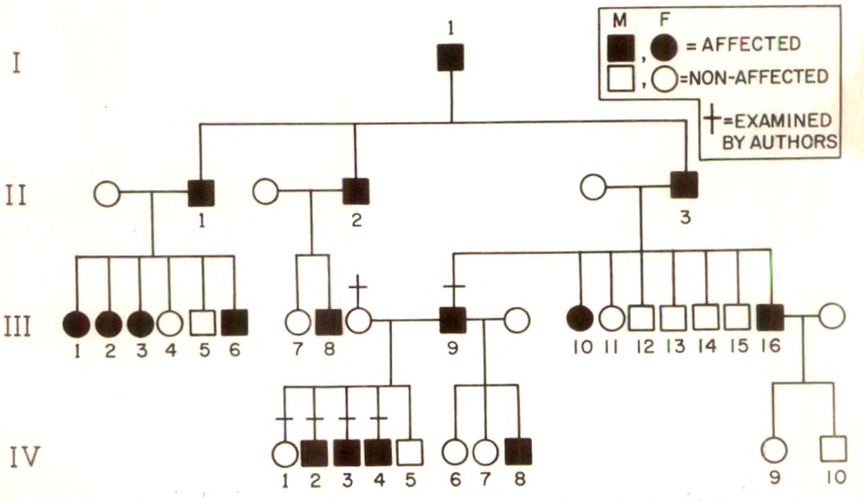



Fig. 2 (Kohn and Romano). Pedigree of the propositi through four generations.

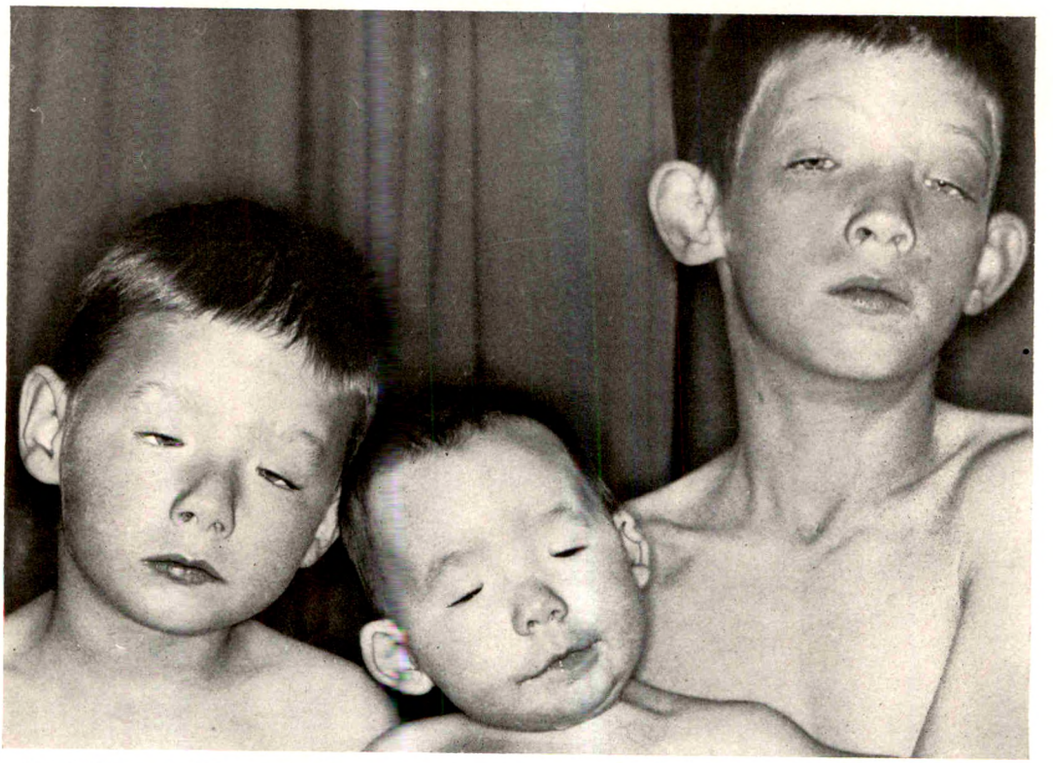


Fig. 3 (Kohn and Romano). Photographs of the three propositi in 1963 (left to right: Case 2, Case 1, and Case 3) at the ages of five, one, and 11 years, respectively.



Fig. 4 (Kohn and Romano). Photographs of the three propositi in 1970 (left to right: Case 2, Case 1, and Case 3) at the ages of 12, eight, and 17 years, respectively.

tently refused surgery. Best corrected visual acuity is RE: 20/200, LE: 20/50 (RE: +2.00 sph.⊃+2.00 cyl. ax. 95° and LE: +2.50 sph.⊃+1.75 cyl. ax. 90°). Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus are present bilaterally and symmetrically. The blepharoptosis is severe, as the upper eyelid crosses the cornea at the lower third of the pupil (in primary position) and levator action is essentially absent (with frontalis immobilized). No eyelid folds are apparent, the tarsal plates feel moderately hypoplastic, and the skin overlying the upper eyelids is smooth and somewhat atrophic. Both eyebrows show increased vertical width. Blepharophimosis is evidenced by a narrowing of the palpebral fissure, both horizontally and vertically (even when frontalis action is maximal). Both caruncle and plica semilunaris are hypoplastic and secluded beneath the epicanthus inversus fold. Telecanthus is clinically present, although the interpupillary distance is unremarkable at 49 mm. The upper eyelid margins assume an S-shape, but the lower eyelid margins are essentially normal. The puncta are normal in appearance and abnormal in location—the lower displaced laterally with respect to the upper which appears displaced medially. The nasal bridge is flat, but bone structure is normal at the supraorbital rims and brows. Both corneal diameters are 10 mm without other evidence of microphthalmos. An esotropia of 20 diopters for near and distance is noted by the Hirshberg and Krimsky tests, along with horizontal endpoint nystagmus. A limitation of duction is present in the field of action of both superior recti, while there is overaction of both inferior obliques. Fundi are entirely normal. There are two additional striking characteristics—a high arched palate and low set ears with deformed pinnas (cupped ears). The child's mentality and school performance are appropriate for his age.



Fig. 5 (Kohn and Romano). Case 1.



Fig. 6 (Kohn and Romano). Case 2.

*Case* 2—This 12-year-old white boy (Figs 3, 4, and 6) was also noted to have "small eyes" since birth. Surgery is consistently refused by the family. Best corrected visual acuity is RE: 8/200, LE: 20/70 (RE: −7.00 sph⊃+1.50 cyl. ax. 180° and LE: −5.50 sph.⊃+2.00 cyl. ax. 180°). Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus are again bilateral and symmetrical. The blepharoptosis is less severe than in Case 1, as the upper eyelid crosses the cornea at midpupil, but levator action is essentially absent. No eyelid folds are apparent, the tarsal plates feel moderately hypoplastic, and the skin overlying the upper eyelids is smooth and somewhat atrophic. Both eyebrows show increased vertical width. Blepharophimosis is evidenced by a narrowing of the palpebral fissure, both horizontally and vertically (even when frontalis action is maximal). The epicanthus inversus is less prominent than in Case 1 with a hypoplastic caruncle and normal plica secluded below. Telecanthus is present, but the interpupillary distance is again unremarkable (54 mm). The eyelid margins are of normal contour, in contrast to Case 1. The puncta appear normal, but the lower is displaced laterally with respect to the upper, which is in relatively normal position. The nasal bridge is flat, but bone structure is normal at the supraorbital rims and brows. Both corneal diameters are 11 mm. An esotropia of 20 diopters is again noted by the Hirshberg and Krimsky tests along with horizontal end-point nystagmus. Both superior recti demonstrate limitation of duction, while both inferior obliques are overactive. This patient demonstrates colobomas of both optic disks. As in the previous case, the palate is high arched, but no ear deformities are present. Mentality and educational performance are normal.

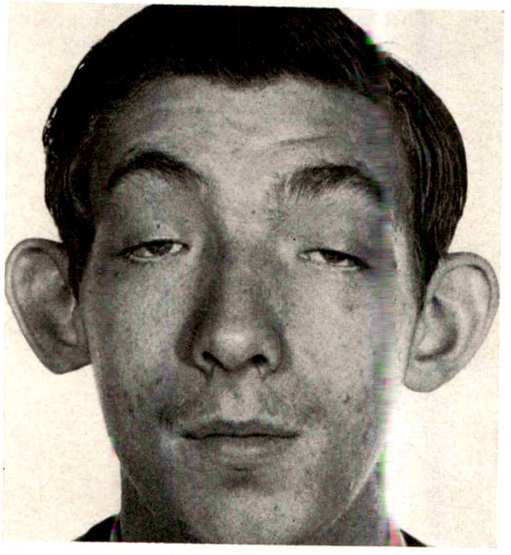


Fig. 7 (Kohn and Romano). Case 3, utilizing the frontalis to raise eyelids.

*Case* 3—This 17-year-old white boy (Figs. 3, 4, 7, and 8), the eldest of these three brothers, was also known to have "small eyes" since birth, and surgery has been refused. Visual acuity is RE: 20/20, LE:20/40, unimproved by refraction or pinhole. Blepharoptosis, blepharophimosis, epicanthus inversus, and telecanthus are bilateral and symmetrical, but the epicanthus is minimally prominent and its inverse character is recognizable only on close inspection. The blepharoptosis is less severe than in Case 1, as the upper eyelid crosses the cornea at midpupil, but levator action is essentially absent. No eyelid folds are present, the tarsal plates are only slightly hypoplastic, and the skin overlying the upper eyelids is smooth and atrophic. Both eyebrows show increased vertical width. Blepharophimosis is evidenced by a narrowing of the palpebral fissure, both horizontally and vertically (even with maximal frontalis action). Both caruncle and plica are moderately hypoplastic and secluded beneath the epicanthus inversus fold. Telecanthus is present along with an interpupillary distance of 67 mm. The upper eyelid margins are S-shaped, but the lower eyelid margins are unremarkable. The puncta appear normal with the lower displaced laterally and the upper displaced medially. The nasal bridge is flat, but bone structure is normal at the supraorbital rims and brows. Both corneal diameters are 11 mm. The patient is orthophoric, but does demonstrate some limitation of duction of both superior recti. No end-point nystagmus is evident. On ductions, the blepharoptosis of each eye is moderately accentuated as that eye is adducted. The fundi of both eyes are normal with the exception of a localized area of pallor inferiorly on the right optic disk. This may represent another coloboma, but it is not as classic as those seen in Case 2. The palate is high arched and the ears are low set with deformed pinnas (cupped ears). Mentality and educational performance are normal.

## Discussion

All three cases demonstrate blepharoptosis, blepharophimosis, epicanthus inversus, telecanthus, and many of the previously reported features associated with the syndrome. In addition, they present several findings not previously reported. These include esotropia with overaction of the inferior obliques, colobomas of the optic disk, and low set, "cupped" ears.

Because of the prominent epicanthus inversus, this syndrome manifests an apparent esotropia. Actually, in Cases 1 and 2, true esotropia does exist along with overacting inferior obliques.

Colobomas of the optic nerve heads are present in Case 2. They are estimated to be 1 mm in diameter (two-thirds of a disk diameter) and appear bilaterally and symmetrically. This may be a factor in this patient's markedly depressed vision in both eyes.

The low set, "cupped" ears are unique features in Cases 1 and 3. In both these pa-

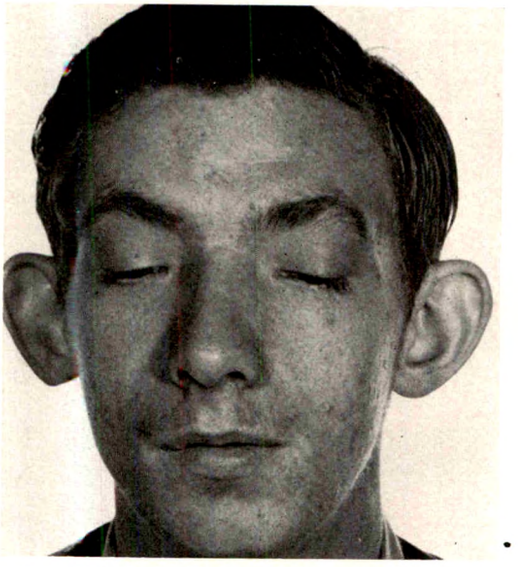


Fig. 8 (Kohn and Romano). Case 3. Note severity of blepharoptosis when patient voluntarily relaxes frontalis.

tients, the ears protrude at right angles from the side of the face, and should be distinguished from "lop ears" which are essentially normal in form, but with the helix folded back upon itself.

Visual deficits, although previously reported, are uncommon and rarely marked. Yet, all three of these cases show some visual loss.

It is not possible to pinpoint a precise cause for the visual loss in each eye because a variety of abnormalities are present which may explain it. In Case 2, for example, the depressed acuity in the right eye is probably due to strabismic amblyopia. But this visual loss may also be due to deprivation amblyopia from blepharoptosis, refractive amblyopia (glasses have not been worn regularly), or anisometropic amblyopia (spherical equivalent difference of 1.75 D.). The boy also has colobomas of the disks of both eyes and small corneal diameters which may contribute to the visual deficiency. Similar factors are present in the other cases as well. Further diagnostic studies are planned to elucidate the causes of these visual deficiencies.

## Summary

The syndrome of blepharoptosis, blepharophimosis, and epicanthus inversus includes many associated anomalies. Chief among these is telecanthus, which is so consistent an association that the disorder should be considered a tetrad including it. The syndrome is inherited as an autosomal dominant with essentially 100% penetrance. To the 125 previously reported cases three more are added, each with unique features—esotropia with overaction of the inferior obliques, colobomas of the optic disk, and low set "cupped" ears.

### Acknowledgment

We thank Dr. David E. Shoch for his comments and advice and Drs. Joseph Alfano, Mary Kaper and Robert Wertz for bringing this family to our attention.

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## Ophthalmic miniature

State Attorney General Louis J. Lefkowitz charged yesterday that an oral test of reasoning "used to select steamfitting apprentices was discriminatory . . ." and that the test had no relation to the skills required in the trade. The Attorney General cited the following illustrations of questions that were put to candidates: (1) What is the relationship of Shakespeare to Othello? (2) What is Brahms to music and Whitman to poetry? (3) How can the relationship of a stag to a doe be compared with that of a ram to an ewe? (4) What is the relationship of Dante to the Inferno?

*New York Times*
Feb. 15, 1971

# IRIS HEMANGIOMA AND ABNORMAL RETINAL VASCULATURE IN A CASE OF DIFFUSE CONGENITAL HEMANGIOMATOSIS

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Generalized cutaneous and visceral hemangiomas in the neonate are a rare and serious phenomenon; there are only eight reported cases.[1,2] This is a report of an infant with diffuse congenital hemangiomatosis; in addition to a unilateral cavernous hemangioma of the iris, retinal vasculature was found to be abnormal bilaterally. In the other affected tissues, the lesions consisted of vascular hamartomas in which abnormally dilated capillaries were sometimes associated with a reduced number of the vessel-wall pericytes.

## CASE REPORT

This black infant girl weighed 3.08 kg at birth on January 5, 1969. The medical history of her 25-year-old mother included asthma, glucose-6-phosphate dehydrogenase deficiency, three normal pregnancies and one unexplained stillbirth. There was no family history of hemangiomas. Pregnancy, induced labor, and delivery were all normal, and no hemangiomas were observed in the placenta.

At birth, however, multiple blue to purple subcutaneous nodules ranging from 1 to 20 mm in diameter were apparent over the infant's scalp, neck, trunk, and extremities. Red sessile hemangiomatous-appearing lesions were seen on the cheek, tongue, leg, and right iris. The discrete iris lesion measured 2-3 mm, had a bright red, irregular surface, and was situated at the iris base at five o'clock (Fig. 1). Chest x-ray films revealed multiple lung nodules. A biopsy of a leg-skin nodule showed a capillary hemangioma. At the time of the skin biopsy, dilated fundus and intraocular pressure examinations of both eyes were normal.

The infant did well for two weeks, but then developed a paralysis of the left arm, a right lateral rectus palsy, blepharoptosis of the left eyelid, and a visibly abnormal enlargement of the head circumference. Repeat chest x-rays revealed enlargement of the previously noted lung nodules. Treatment with oral prednisone at 3 mg/kg/day was begun and continued for three weeks. The electroencephalogram was normal, but a brain scan showed bilateral superficial areas of uptake, being more prominent on the right side than the left. A cerebral arteriogram revealed only moderate hydrocephalus. The skull continued to enlarge, and separation of the cranial sutures was seen on x-ray. A bulging anterior fontanelle, vomiting, and lethargy developed. A right ventricular tap showed increased pressure and xanthochromic fluid. A pneumoencephalogram revealed two-pedunculated lesions in the lateral ventricles, and posterior and lateral displacement of the aqueduct, suggesting a midbrain mass. The four-week-old infant rapidly declined, presenting bilateral lateral rectus palsies, bilateral wrist drops, and a right foot drop. A ventriculoperiotoneal shunt was attempted, but failed. The infant developed meningitis, subsequently experienced periods of intermittent apnea and tachycardia, and died at the age of 35 days.

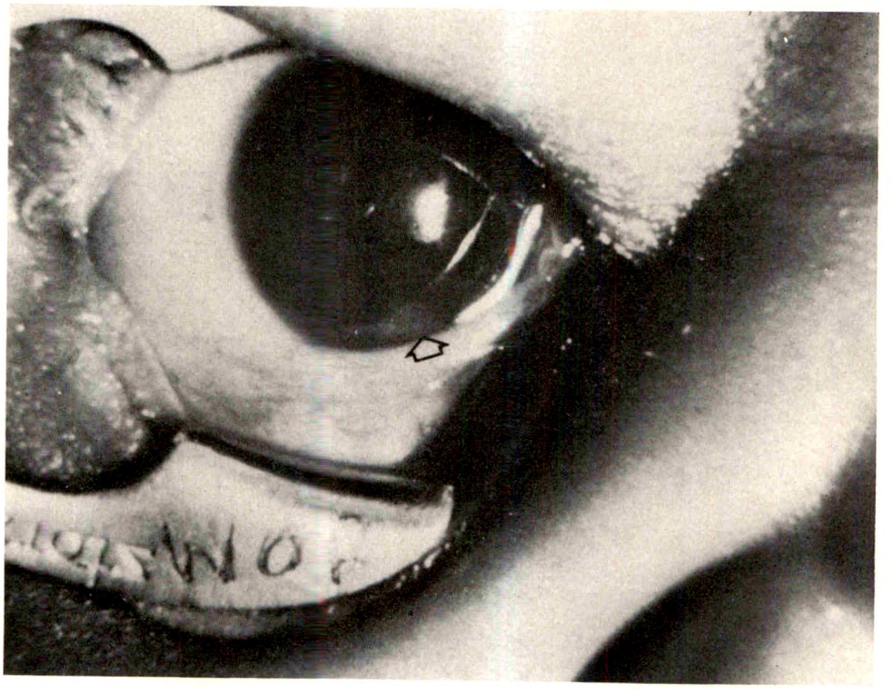
## PATHOLOGY

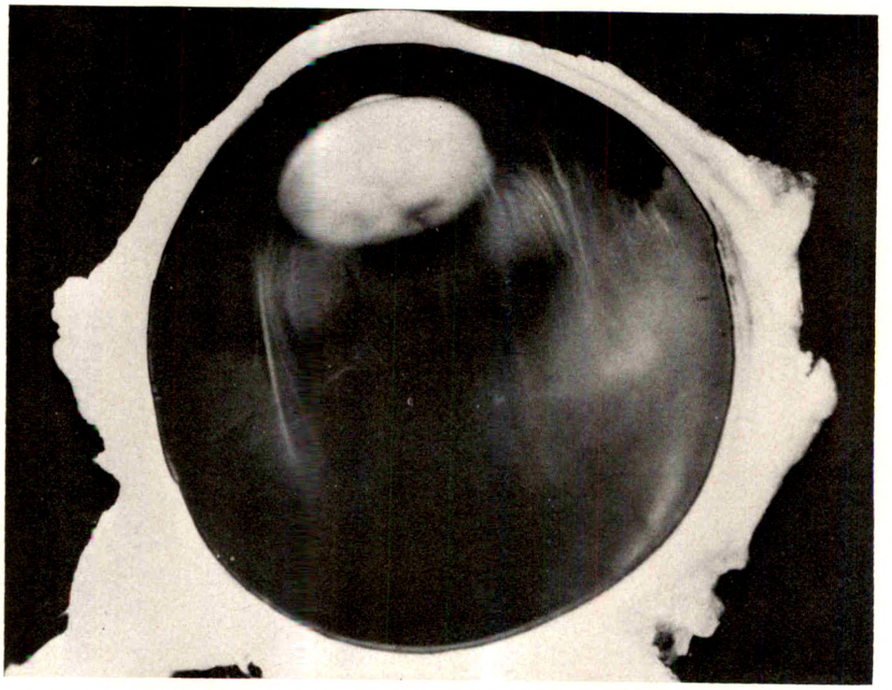
Postmortem examination disclosed hemangiomas in the skin, subcutaneous tissue, esophagus, stomach, intestine, mesentery, mesocolon, lungs, diaphragm, bladder, lymph nodes, cervix, muscle, heart, thymus, larynx, tongue, kidney, spinal cord, meninges, brain and iris. Hemangiomas at the roots of C-7, C-8, T-1 and the lumbosacral regions of the spinal cord correlated well clinicopathologically with the brachial palsies and the foot drop, as did the marked hemangiomas of the midbrain and pons with the third and sixth nerve palsies, and the aqueduct compression by midbrain hemangiomas with the dilated third and lateral ventricles.

*Ocular tissues*—On gross examination, the right eye measured 18 × 19 × 19 mm, with 12.5 mm of optic nerve attached. The cornea measured 10.5 × 10 mm. The pupil was round and central and measured 3.5 mm in diameter. There was a ring of limbal pig-

From the Eye Pathology Laboratory, Department of Pathology and the Wilmer Institute, Johns Hopkins University and Hospital. This investigation was supported in part by Public Health Service Postdoctoral Fellowship 1 FO2 EY48611-01 from the National Eye Institute (Dr. Kenyon).

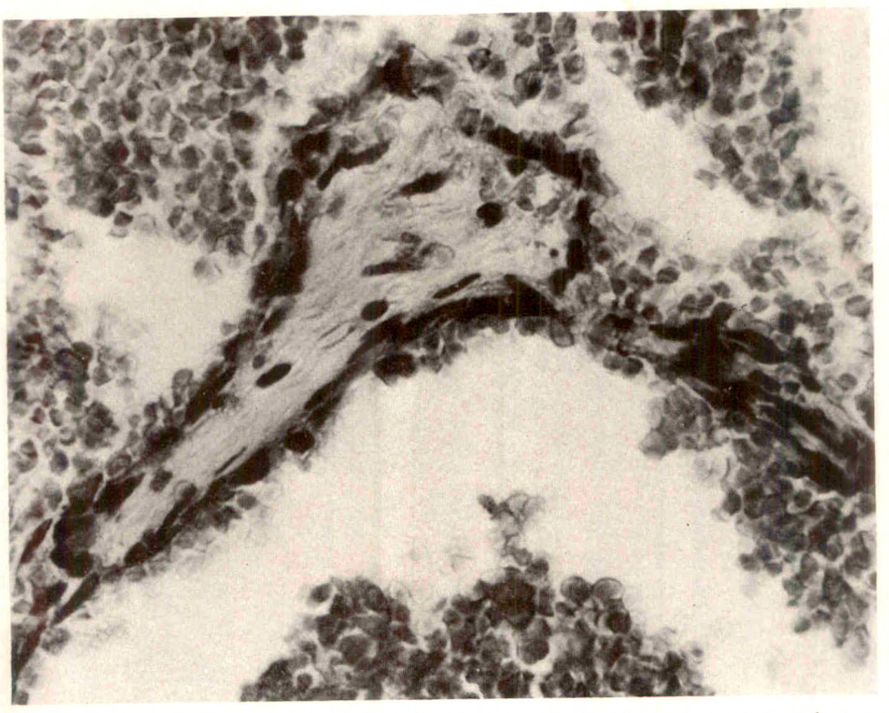
Reprint requests to W. Richard Green, M.D., Eye Pathology Laboratory, Johns Hopkins Hospital, Baltimore, Maryland 21205.



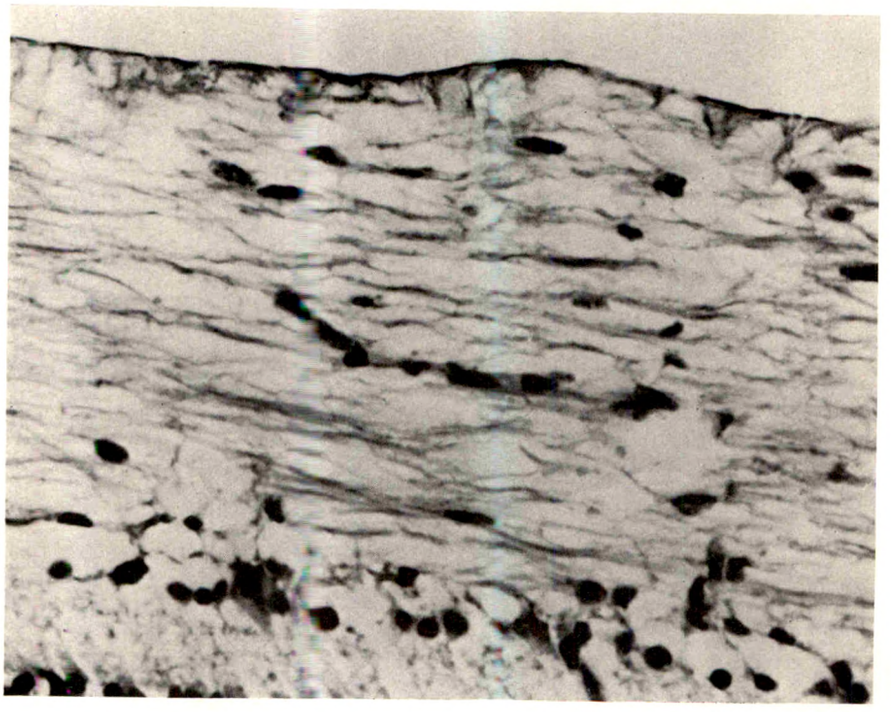


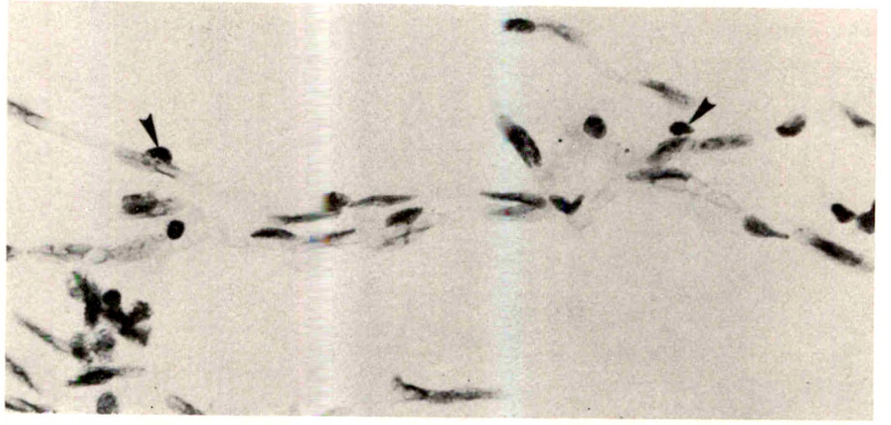
Figs. 1 and 2 (Naidoff, Kenyon, and Green). Figure 1 (top): The hemangioma (arrow) is situated at the iris base in the five o'clock position. Figure 2 (bottom): In the area of the iris hemangioma, notching of the lens is evident upon gross examination (×4).



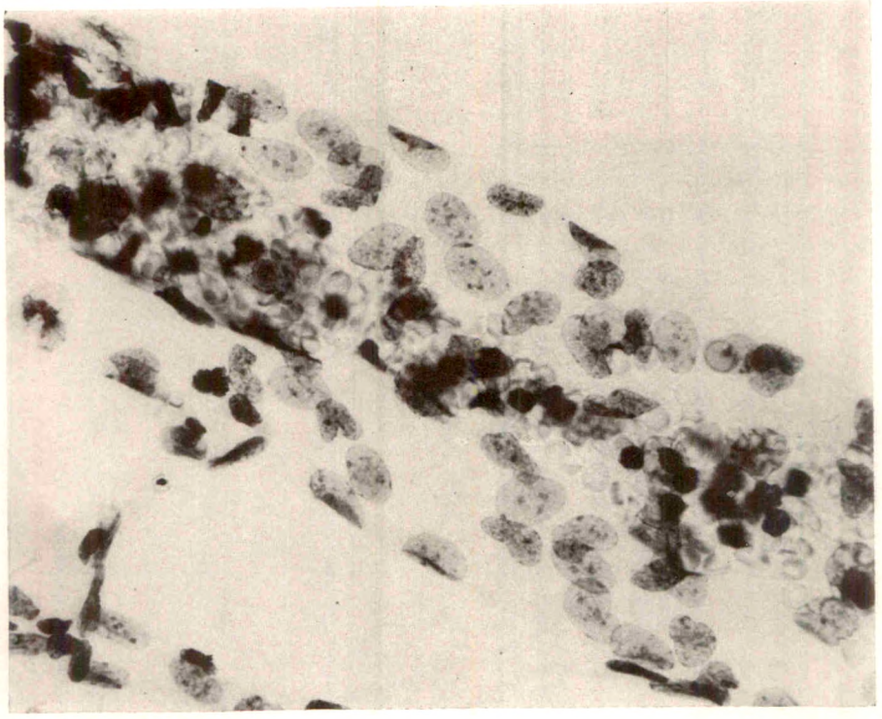


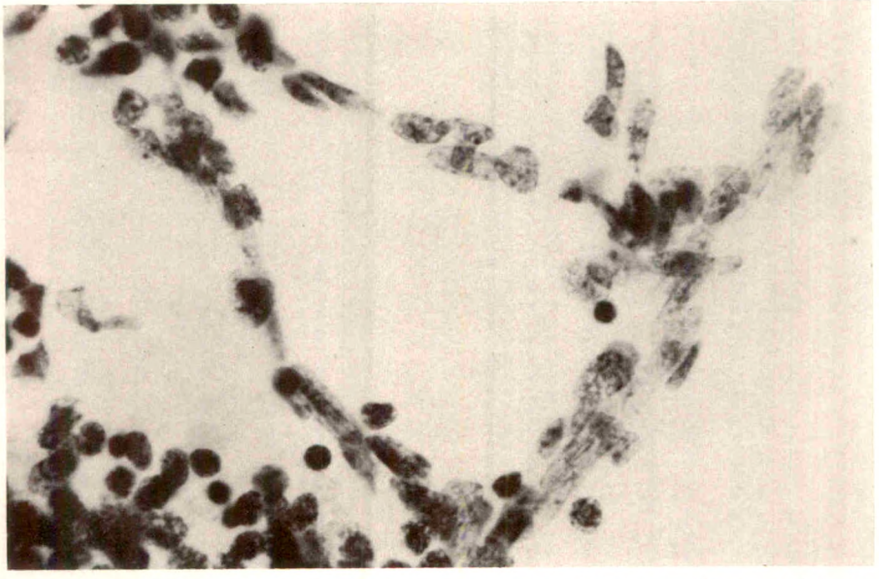
Figs. 3 and 4 (Naidoff, Kenyon, and Green). Figure 3 (top): In histologic section at low magnification, the hemangioma of the peripheral iris stroma is shown occluding the angle and compressing the ciliary body (hematoxylin-eosin, ×135). Figure 4 (bottom): At higher magnification, histologic section of the iris hemangioma reveals dilated vascular channels lined by endothelial cells and traversed by connective tissue septae (hematoxylin-eosin, ×520).





Figs. 5 and 6 (Naidoff, Kenyon, and Green). Figure 5 (top): In histologic sections of the retina, blood vessels are reduced in frequency and appear to consist of endothelial cells only (hematoxylin-eosin, ×550). Figure 6 (bottom): In trypsin digest preparations of the retina, the few remaining retinal capillaries demonstrate a conspicuous reduction of perithelial cells (arrowheads) in association with a prominent or increased endothelial cell population (×550).





Figs. 7 and 8 (Naidoff, Kenyon, and Green). Figure 7 (top): This larger blood vessel in the trypsin-digested retina appears as a cylinder of pure endothelium which is totally devoid of pericytes (×600). Figure 8 (bottom): In the retina of the fellow eye (os), trypsin digestion discloses similar vascular abnormalities including reduction of vessels, prominence of endothelial cells and deficiency of pericytes (×875).

mentation which was particularly prominent at the five o'clock position. No defects were seen on transillumination. A 3 mm tumor was present at the iris base at five o'clock. After the globe was sectioned vertically, the pigmented iris lesion appeared to be either compressing the ciliary body or infiltrating it and thus obstructing the angle. The lens was notched inferiorly (Fig. 2), and also showed normal posterior umbilication. Small pigment clumps were seen on the zonules. The optic disk was normal. The left eye measured 17.5 × 17 × 17 mm and was normal.

Examination of histologic sections of the right eye revealed a normal cornea. Serial sections numbered 1 through 143 disclosed a lesion composed of large thin-walled vascular structures filled with blood in the inferior iris leaf (Fig. 3). The vascular lesion was located in the iris stroma at the periphery, where it occluded the angle anteriorly, compressed the ciliary body posteriorly and notched the lens superiorly. The channels coalesced to form even larger vascular spaces which were lined by plump and, in some areas, flattened endothelial cells with little or no intervening fibrous tissue (Fig. 4). No muscular tissue was observed in the walls of the vessels by routine and special staining techniques. The iris pigment epithelium was intact and the remaining iris was normal.

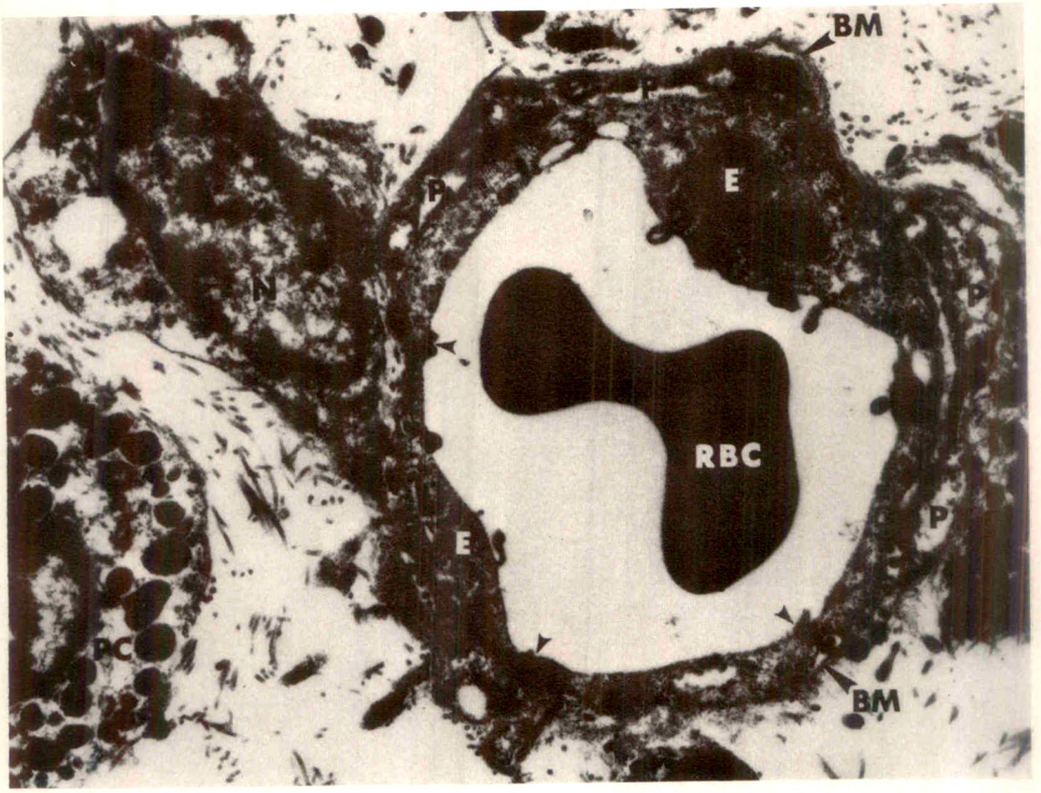
The retina appeared normal on routine sectioning except for a decreased number of vessels, which had unusually thin walls and demonstrated endothelial cells only (Fig. 5). Portions of retina from both eyes were subjected to trypsin digestion. This disclosed a curious finding, in that both specimens almost completely disintegrated when exposed to the action of trypsin for short periods of time. In a few areas where the retinal vasculature remained relatively intact, there was a conspicuous reduction or absence of intramural pericytes, with a prominent to increased number of endothelial cells (Fig. 6 and 7). Some totally avascular areas were observed. The optic disk and nerve were normal. Histologic examination of the left eye was normal except for the previously noted retinal vascular abnormalities (Fig. 8).

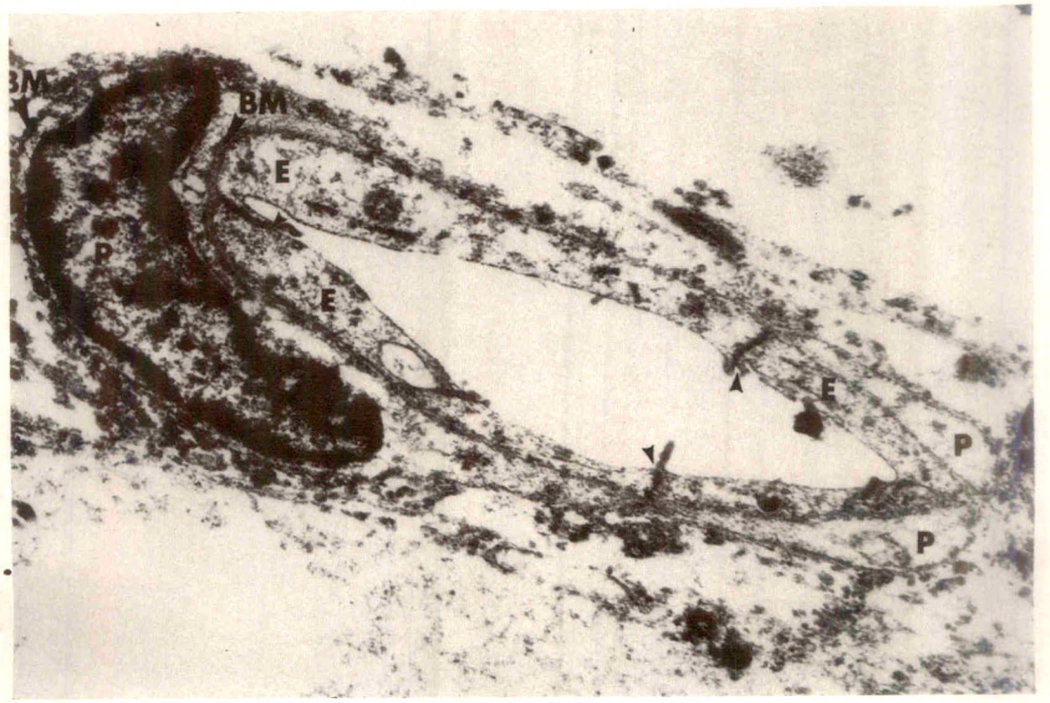
For detailed study of vascular ultrastructure in the ocular tissues of this patient, the formalin-fixed and paraffin-embedded histologic material was reprocessed for electron microscopy by dissolution of the paraffin with chloroform, rehydration in veronalacetate buffer, dissection into suitably sized specimens, fixation in veronal-acetate-buffered 2% osmium tetroxide, and embedding in Araldite epoxy resin. Thin sections were then cut on a Porter-Blum MT-2 microtome, doubly stained with uranyl acetate and lead citrate, and examined with a JEM 100-B electron microscope.

The cavernous hemangioma of the iris could not be surveyed by electron microscopy because it had been serially sectioned in its entirety for histologic examination. In the unaffected portion of the iris and in the histologically unremarkable ciliary body, however, the capillaries appeared to be entirely normal, as they exhibited a continuous endothelial lining and a normal complement of



Figs. 9 and 10 (Naidoff, Kenyon, and Green). Figure 9 (top): In this electron micrograph, a capillary of the iris is shown to possess a continuous lining of endothelial cells (E) joined by tight junctions (arrowheads). Several pericyte processes (P) are embedded in the basement membrane (BM) of the endothelium. The nucleus (N) of a large perithelial cell is prominent, as are the erythrocyte (RBC) in the vessel lumen and the pigment cells (PC) of the iris stroma (×11,000). Figure 10 (bottom): By electron microscopy, the ultrastructure of this retinal capillary is essentially normal. The endothelial cells (E) are connected by tight junctions (arrowheads). Well-developed pericytes (P) are enveloped by the endothelial basement membrane (BM) (×11,000).


BM
E
P
N
RBC
E
P
PC
BM


BM
BM
E
P
E
E
P
P

perithelial cells which were enveloped by the basement membrane of the endothelial cells (Fig. 9).

The ultrastructural alterations of the retinal capillaries were generally consistent with the abnormalities evident in the histologic and trypsin digest preparations. In particular, the retinal vessels were found to be markedly reduced in frequency throughout the retina; and in distribution, they were essentially limited to the nerve fiber layer and ganglion cell layer, with virtual absence of capillaries in the inner plexiform and nuclear layers. Whereas the majority of these capillaries displayed the usual ultrastructural appearance of endothelial cells and associated pericytes invested by a basement membrane (Fig. 10), in perhaps one-third of the retinal capillaries, no intramural pericytes could be identified (Fig. 11). The caliber of these vessels was within normal limits and was seemingly unrelated to the presence or absence of pericytes.

In the choroid, the endothelial and perithelial cells of the choriocapillaris appeared normal. No abnormalities of the retinal pigment epithelium or Bruch's membrane could be demonstrated by electron microscopy.

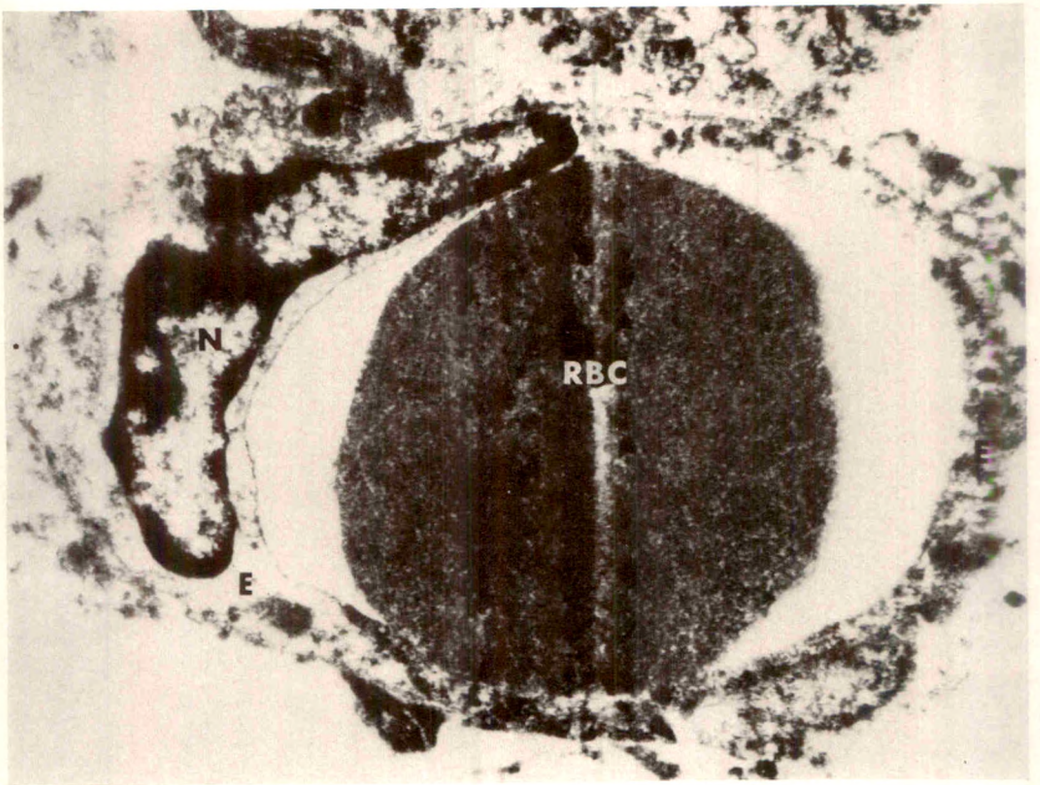
*Other tissues*—The histologic appearance of the cutaneous and visceral hemangiomas varied from capillary to cavernous types, which consisted of dilated thin-walled channels lined by a single layer of endothelial cells, without obvious endothelial proliferation or arteriovenous connections. A particularly interesting finding was that no pericytes could be demonstrated by Bodian silver stain.[1]

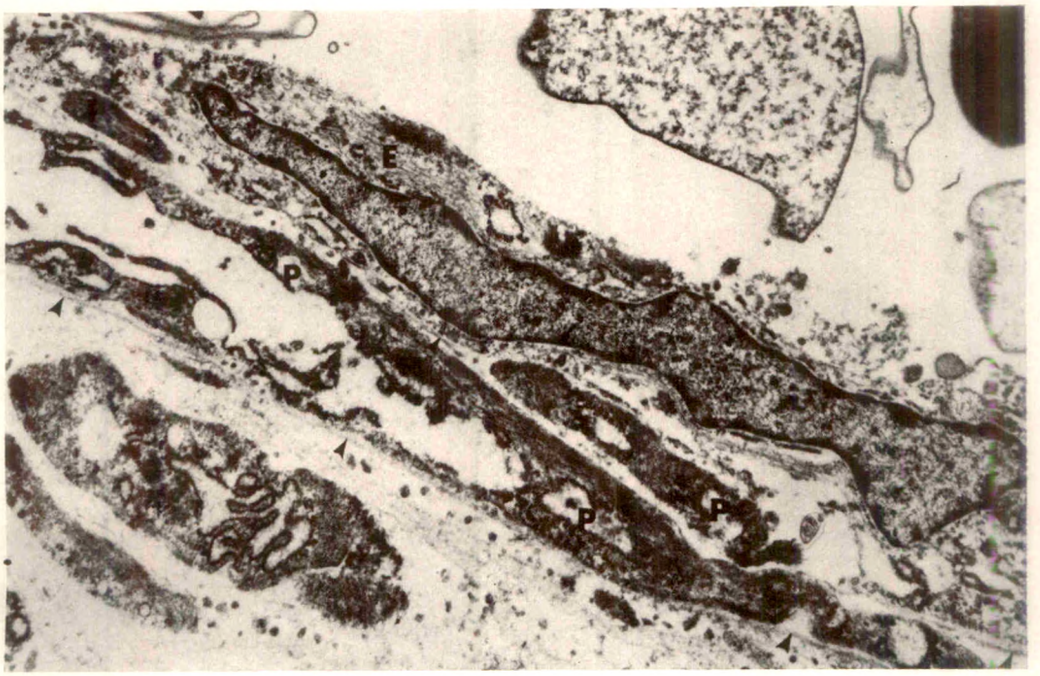
In an attempt to establish the significance of this latter finding, hemangiomas from the liver, kidney and heart tissues were studied by electron microscopy. (These specimens, which had been formalin-fixed but had not been embedded in paraffin, were prepared for electron microscopy by the previously described techniques.) In the cavernous hemangiomas of the liver parenchyma, the pericytes could be identified with certainty, as they were closely associated with the endothelial cells and were clearly invested by a well-developed basement membrane (Fig. 12). In the hemangiomas of the renal cortex and superficial endocardium, however, pericytes could not be demonstrated with certainty. Although cells of the appropriate ultrastructural type were apparent in the collagenous tissue surrounding these hemangiomas, such cells were not always in close apposition to the endothelium and, more important, they lacked a clearly defined basement membrane by which they might have been distinguished from connective tissue cells (Figs. 13 and 14). Review of histologic sections from these same specimens were generally consistent with the electron microscopic findings.

## Discussion

All eight reported cases of congenital diffuse hemangiomatosis have resulted in death of the infants before one year of age, the mean survival time being 71 days.[1] The most common cause of death has been heart failure associated with a large liver hemangioma. The cause of death in this patient was attributed to hydrocephalus and meningitis. The unique features of this case were the generalized involvement of the spinal cord,

Figs. 11 and 12 (Naidoff, Kenyon, and Green). Figure 11 (top): Electron microscopy of the retina also reveals abnormal capillaries which are without definite evidence of pericytes despite the presence of a complete endothelial lining (E). (N) nucleus, (RBC) erythrocyte (×19,000). Figure 12 (bottom): In this cavernous hemangioma of the liver parenchyma, electron microscopy permits identification of at least three pericytes (P) which are closely associated with the flattened endothelial cells (E) and are invested by a well-defined basement membrane (arrowheads) (×11,000).


N
RBC
E


E
P
P
P

thymus, uterine cervix, skeletal muscle, and iris, none of which was reported in the previous cases.

Both cavernous and capillary hemangiomas of mixed types have been noted at birth or shortly thereafter and tend to enlarge for three to six months. Reduction in size of these angiomas usually begins by one year of age. The capillary type is usually gone by five years of age; the cavernous type is more variable, less predictable, and more often requires surgical intervention. Zarem and Edgerton[3] reported that the use of oral steroid therapy led to the rapid cessation of growth and partial resolution of capillary and cavernous hemangiomas in children. They postulated that the immature vascular tissue in these hemangiomas was responsive to the anti-anabolic effect of the steroids, usually within two weeks of treatment. However, no beneficial effects of this treatment were noted in the present case.

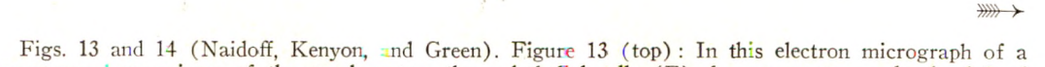
Hemangiomas of the iris are rare. In a series of 145 primary tumors of the iris, Ashton[4] found only three angiomas, an incidence of 2%.

Many cases reported to be iris hemangiomas in the past[5-7] on re-examination have proven to be juvenile xanthogranulomas or malignant melanomas.[8] Reese[9] and Ashton attributed the first histologically proven case of iris hemangioma to Rodin[5] (1929), who also reviewed the nine cases present in the literature at that time and accepted only three as correctly diagnosed. He considered the other six to be granulomas, granulation tissue, or spindle cell sarcomas. However, Rodin's case has now been reclassified as juvenile xanthogranuloma by Dr. Lorenz Zimmerman at the Armed Forces Institute of Pathology.[8]

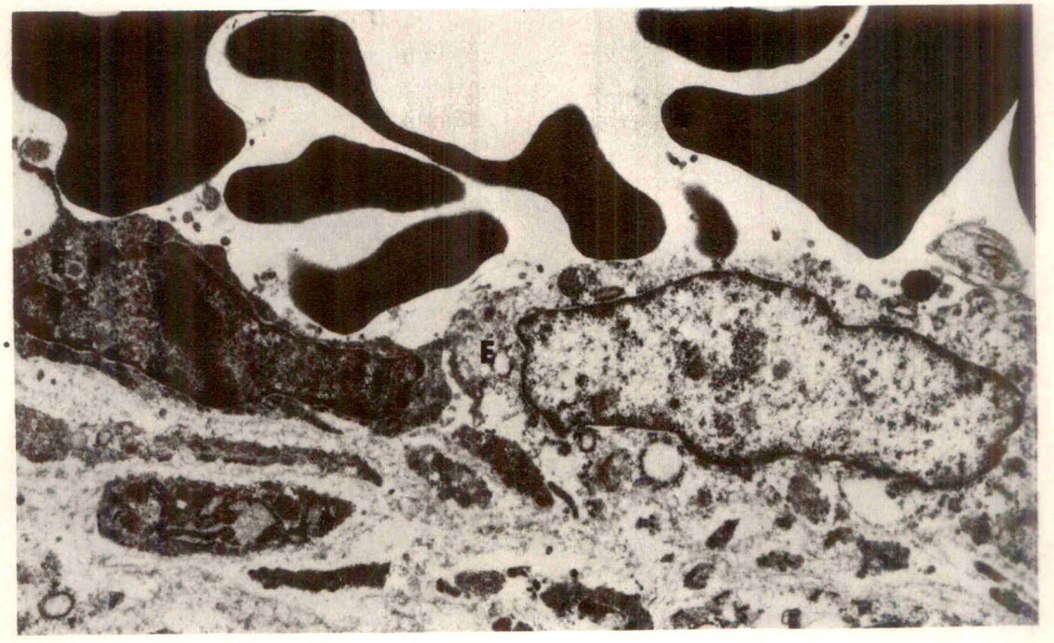
It was not until 1949 that Blank, Eglick, and Beerman[10] showed that juvenile xanthogranuloma could affect the iris and ciliary body. In this condition, the lesions show infiltrates of pale-staining, mononuclear histiocytes replacing the normal iris stroma and leading to focal or diffuse thickening; Touton giant cells and eosinophils are also present. In many cases, multiple thin-walled capillaries are seen, rupture of which accounts for the spontaneous hyphemas seen in this disease. Associated skin lesions are not always present.

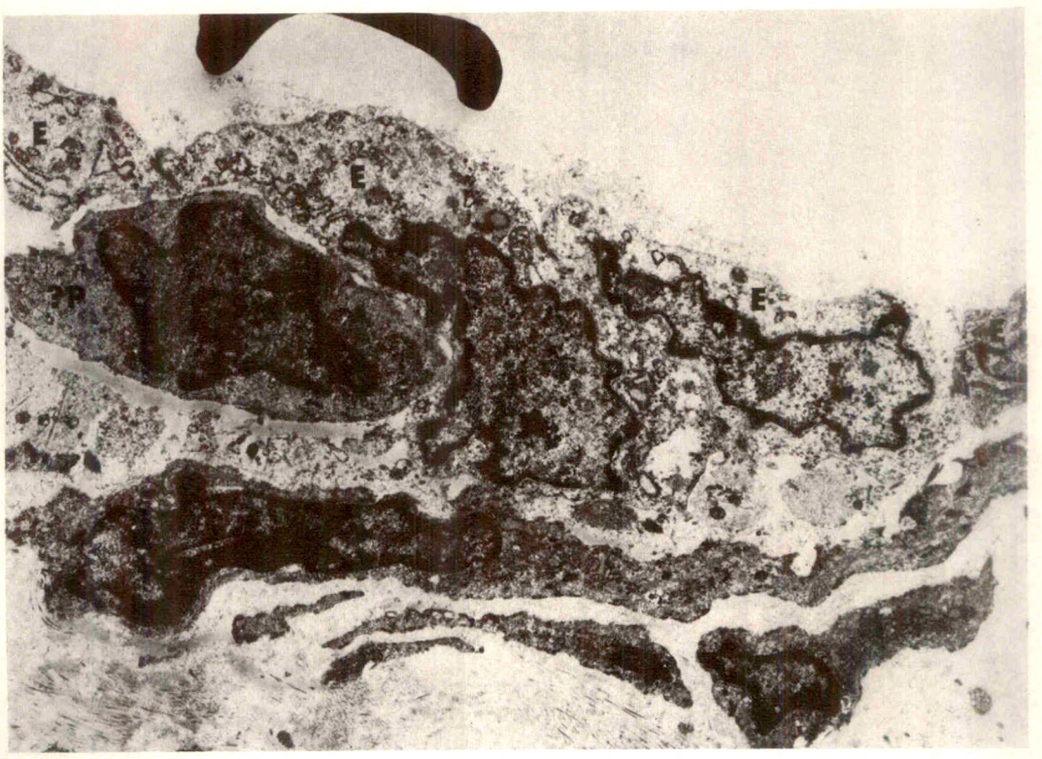
Hogan and Zimmerman[11] state that in iris melanomas, "cystic degeneration, bleeding in the cysts, and hemorrhage into the anterior chamber" may lead to a mistaken diagnosis of iris hemangioma. Moreover, the sometimes marked vascular proliferation in iris melanomas may tend to be more prominent histologically than the melanoma itself.[12] Baghdassarian and Spencer[7] stated that a case reported to be iris hemangioma by Spencer[6] in 1963 was subsequently found to be a melanoma on further sectioning. The important point is that the study of serial sections of suspected iris hemangiomas may instead reveal other entities.

Clinical information in the cases reported as iris hemangiomas is scanty in many instances. These lesions have usually presented with a history of hyphema, though there was no intraocular hemorrhage in our patient. These iris lesions have appeared in patients as young as two months, though most appear in adults. They are usually located near the pupillary border and have a



Figs. 13 and 14 (Naidoff, Kenyon, and Green). Figure 13 (top): In this electron micrograph of a cavernous hemangioma of the renal cortex, the endothelial cells (E) do not possess a clearly defined basement membrane. The cells within the underlying collagenous connective tissue cannot be characterized as pericytes (×8500). Figure 14 (bottom): In the endocardium, electron microscopy demonstrates hypercellularity of the endothelial lining (E) of this cavernous hemangioma. No basement membrane is evident, and pericytes (?P) cannot therefore be unequivocally identified (×6300).


E
E


E
E
P
E

variable history concerning size, with some enlarging gradually and others rapidly. They are described as being red to reddish-white in color and may be present from short to long periods of time. In the recent reports of Ashton,[4] Cashell,[13] and Stallard,[14] the specimens have been obtained by iridectomy.

Histologically, the iris hemangiomas have varied from the capillary type to more cavernous types with delicate fibrous stroma and varying amounts of hemorrhage.

An especially interesting aspect of this case is the histologic and electron microscopic finding of a deficiency of vessel wall pericytes in many of the ocular and visceral tissues. In the eye, although the capillaries of the iris and ciliary body were ultrastructurally unremarkable, the strikingly decreased number of retinal vessels and the extreme fragility of these vessels following trypsin digestion seemed to correlate with the marked reduction in intramural pericytes. In the visceral tissues, the unequivocal presence of pericytes in the cavernous hemangiomas of the liver was in contrast to the lack of identifiable pericytes in the renal and endocardial hemangiomas.

In their discussion of the present case, Holden and Alexander[1] postulated that the hemangiomas may have enlarged secondarily by dilatation of true capillaries in which the absence of pericytes resulted in a loss of tone. And conversely, Kuwabara and Cogan[15] have indicated that the structural integrity of retinal capillaries is dependent upon intact pericytes rather than endothelial cells. Whatever the pathogenesis of these hemangiomatous lesions, it is evident that the observed deficiencies of vessel-wall pericytes points to a generalized congenital defect in capillary structure.

## Summary

Hemangiomas of the iris are rare and have been confused in the past with melanomas and juvenile xanthogranulomas. In a neonate with cavernous hemangioma of the iris, this was associated with generalized cutaneous and visceral hemangiomas, another uncommon phenomenon. Routine and special histologic techniques, plus electron microscopy, disclosed a marked reduction in the number of pericytes in these lesions; the trypsin-digested preparations of the retina showed an almost total absence of intramural pericytes.

### Acknowledgments

We thank Drs. A. E. Maumenee and John Yardley for critical review of this manuscript, and Mr. David Andrews for helpful editorial suggestions.

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## NEW SURGICAL LIGHT

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*New Haven, Connecticutt*

Fiber optic illumination has the unique advantage of bringing adequate light to areas that larger light sources cannot. An operating light source was constructed which combined both specific as well as general field illumination. For specific illumination, we attached a fiber bundle divided into four segments onto a Maumenee eyelid speculum (Fig. 1).

The advantages of using this arrangement are several: The light energy that is delivered is cool and not hot, which is important for a light source this close to the eye. The direction of the light can be altered individually for each case by adjusting the eyelid blade and tightening the clamp. The amount of light is governed by a rheostat on the light source box. The fiber bundles are extremely light and flexible so no added tension or weight is placed on the eye. The brightness of these four ports, as well as the size of the field covered has proved more than adequate (Fig. 2).

For general illumination with this instrument, we used a full-sized fiber bundle with a condensing lens and goose-neck carrier. The goose-neck allows the light to be properly directed and to remain in that position after the bundle is attached to the drape. The condensing lens concentrates the light in an area more nearly approximating the operative field.

The combination of the two lights gives

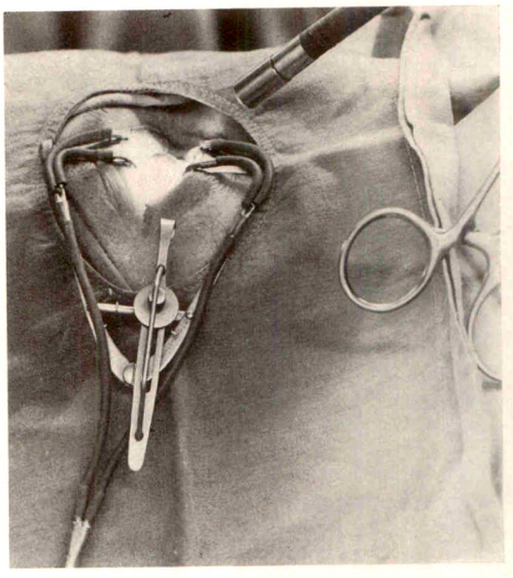


Fig. 1 (Walsh). Lighting of operative field with both types of illuminators.

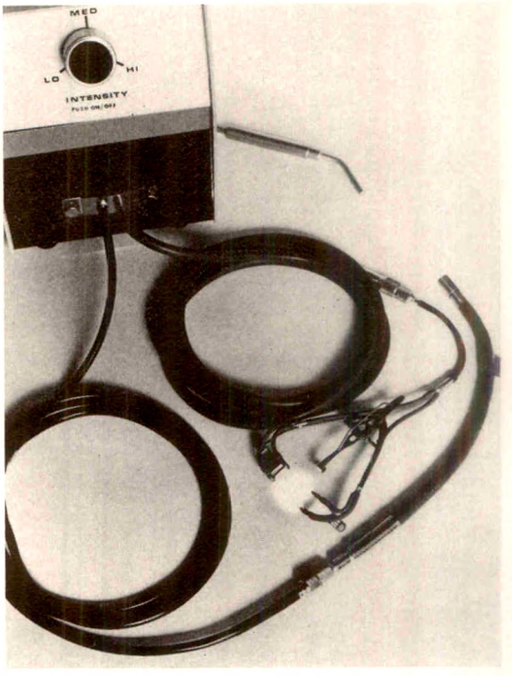



Fig. 2 (Walsh). Light source and all three attachments, including the focal illuminator.

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excellent illumination without shadows and without getting in the surgeon's way as he operates. The entire unit can be sterilized in the autoclave or by gas and cold sterilization methods. The unit comes with a standard third component also—a transilluminator (Fig. 2).

Additional fiber optic attachments are under consideration and development and can be added to the basic unit in the future. The instrument is called Lumi-Trac (Instrumentation for Medicine, Inc.).


## Summary

A new fiber optic surgical light incorporates both general field lighting and focal illumination of the specific operative area. It casts bright illumination without shadows, and is constructed in such a way that it is adaptable to each individual case; the brightness may be adjusted to individual requirements. It is light in weight and causes no traction on the globe, and the whole unit can withstand autoclaving, or it may be sterilized by gas or cold sterilization methods.


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## Ophthalmic miniature

The eye is the most sensitive of all body organs. Therefore it is proper that one drip medications into it extremely gently after having slightly raised the upper eyelid. One should dissolve these medications in liquids that are usually nonirritating. Ancient physicians found egg albumen to be of great benefit as a base for eyedrops.

Maimonides (1135–1204 B.C.)
*Aphorisms*
Am. J. Surg. 119: 721, 1970

# MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

## THE IOWA EYE ASSOCIATION

The annual meeting of the Iowa Eye Association was held in Iowa City on May 12-14, 1971. Three half-day sessions were devoted to clinical papers by present and former residents and staff members. Workshops were offered on vertical muscle imbalances, macular lesions, infectious diseases, and glaucoma. The highlight of this year's meeting was a dinner dance which honored two professors who will soon retire from the University of Iowa faculty, Drs. Hermann Burian and Paul Boeder. The unique contributions of each gentleman to the University of Iowa and to world ophthalmology were recalled, and gifts symbolizing the affection and esteem of their students were presented. Special recognition was given to Dr. Burian by the American Association of Certified Orthoptists.

Frederick Mausolf described the hyperviscosity syndrome in a patient with multiple myeloma. Waxing and waning of retinopathy (hemorrhages, microaneurysms, venous dilatation, and slowed retinal circulation) were correlated with plasmaphoresis-induced changes in plasma viscosity and protein levels.

H. Stanley Thompson discussed the value of pilocarpine in distinguishing atropine-induced mydriasis from paralytic mydriasis. Particular emphasis was placed on Jimson weed toxicity. The Jimson weed, containing belladonna alkaloids, is a common invader of crop fields and causes the "corn picker's pupil." Richard Falter reported pharmacologic and pupillographic studies of the mechanism of the initial mydriasis caused by topical guanethidine.

Paul Rutkowski reported that increased intraocular pressure in humans, produced by a suction cup ophthalmodynamometer, causes mydriasis. Impairment of the iris sphincter can be demonstrated by pupillography. Iris fluorescein angiography shows no apparent filling of iris vessels at intraocular pressures above the diastolic ophthalmic artery pressure.

Richard Ulrich gave a progress report on a method originally developed by Donald Greif for recording electroretinograms and occipital lobe electrical responses after stimulation of isolated retinal areas. This technique may become useful for objective visual field examination.

Adnan Halassa reviewed the effect of glaucoma on the blood supply to the optic disk. Fluorescein angiography demonstrated an improvement in circumpapillary choroidal filling following lowering of ocular hypertension by osmotic agents.

Bruce Spivey discussed new methods of teaching ophthalmology to medical students, including self-instruction units and teaching mannekins. Ronald Zahoruk demonstrated the use of television as a teaching aid for external, slit lamp, and fundus information in neuro-ophthalmology.

Karel Maertens, visiting from the Lovanium University in Kinshasa, Democratic Republic of the Congo, portrayed the vicissitudes of practicing ophthalmology in the Congo and described parasitic eye diseases which are virtually unknown to American ophthalmologists.

Bruce Bedell reviewed current research being conducted by the Army Laser Safety Team in Philadelphia. Ogden Frazier and Lee Allen described experiments in filter combinations for color fluorescein fundus angiography.

Philip Knapp described several useful techniques for strabismus surgery when there are extensive adhesions from previous surgery. Particular emphasis was placed on marginal tenotomies, bare sclera technique,

and use of Supramid Extra sleeves and sheets between muscle and sclera to prevent reformation of adhesions.

Robert Watzke presented several cases of intraocular tumors which had defied usual clinical dictums. Larry Wood described the clinical and pathologic findings in a case of Wegener's granulomatosis involving the eyes.

Thomas Burton studied how long it took to freeze the ciliary body of a normal human eye which was subsequently removed as part of an orbital exenteration specimen. By indenting the sclera with the freezing probe he could directly observe blanching of the ciliary processes. Although freezing began with equal rapidity at probe temperatures of −45° and −75° C, the colder temperature proved much more destructive when the lesions were examined histologically; 60 seconds was the optimal freezing time.

Donald Doughman reviewed the Stevens-Johnson syndrome and described the management of its late ocular effects, especially deficiency of mucus in the tears. A scleral contact lens combined with artificial tears is the most successful treatment.

James Allen reviewed the treatment of chronic facial nerve paralysis and described a temporalis muscle-facial transplant to restore eyelid closure.

Frederick C. Blodi presented a review of current department activities and described plans for future expansion. He also presented a series of clinical-pathologic mystery cases which tested the wit and acumen of the audience.

At a brief business meeting, President Joseph Dvorak turned the association's leadership over to new President Arthur Wise. Landis Stewart is the new President-Elect and Charles Phelps the new Secretary-Treasurer, replacing Bruce Spivey, who resigned after nine years of faithful service.

Charles D. Phelps

## UNIVERSITY OF TORONTO ANNUAL RESEARCH MEETING

The 13th annual research meeting and clinical day of the Department of Ophthalmology of the University of Toronto was held May 13-14, 1971. The guest speaker on Research Day was Matthew Alpern, professor of physiological optics in the department of ophthalmology at the University of Michigan. The Clinical Day guest speaker was Arnold Forrest, clinical professor of ophthalmology at Presbyterian Hospital, New York City. Abstracts of the papers presented are as follows:

### AVIAN MACROPHTHALMOS WITHOUT OCULAR HYPERTENSION

Drs. K. Axmith and J. D. Morin (Toronto)—After 128 domestic chickens were reared in continuous incandescent light for 16 weeks, beginning at one week of age, random assignment was made to seven equal groups—six treatment groups and a control group. Surgical treatment comprised unilateral optic nerve section and thermal sclerectomy. Others received atropine 1%, epinephrine 1% drops to the right eye, or epinephrine drops plus acetazolamide in the feed. A control group received no medication. At the end of the treatment period intraocular pressure (IOP) and outflow facility (C) were determined manometrically, using a constant infusion pressure technique. Mean IOP was 7.59 mm Hg. Mean C was 0.05 ml/minute/mm Hg. Mean eye weight was 4.6 g. There was no difference between right and left eye parameters in any group. The only significant difference seen was in IOP between the control group and those submitted to optic nerve section. In no case was there microscopic evidence of pressure-induced pathology. Medical and surgical treatment did not alter the course of eye enlargement. Bilateral eye enlargement occurred with lowered C but without increased IOP in any eye. It was concluded that so-called avian buphthal-

mos does occur in continuous light, but this phenomenon is not related to raised intraocular pressure.

### Role of platelets in corneal graft reaction

Drs. J. J. Hurwitz and P. K. Basu (Toronto—Platelet concentrations in the systemic and limbal circulations and in the aqueous humor were studied in rabbits receiving interlamellar corneal xenografts. A new technique was described for obtaining platelets from the limbal circulation. Results showed that after a rise during the "latent period" there is a marked fall of platelets coincident with the onset of graft rejections.

When heparin was used intramuscularly every 12 hours, the onset of graft rejection was delayed and the severity of reaction diminished.

### Enzymatic zonulolysis using fibrinolytic enzyme

Drs. I. Melnyk and L. D. J. Chisholm (Toronto)—It is well recognized that alpha chymotrypsin will not dissolve the lens-vitreous attachments in children or young rabbits. To determine its effects on intracapsular lens extractions in rabbits, a fibrinolytic enzyme, CA-7, was used in three different concentrations for enzymatic zonulolysis in the same manner as alpha chymotrypsin is used. Operative results showed that while vitreous loss was inevitable without CA-7; with it, however, lens extraction was performed in many of the eyes without vitreous loss. Clinical observations were continued for six weeks postoperatively, and pathologic studies were conducted.

### Effect of vitamin A deficiency on the incorporation of glucosamine in the rat retina

Drs. R. D. Merritt and Y. Matuk (Toronto)—The incorporation of radioactive glucosamine into the protein of subcellular portions of retinas (smooth, rough microsomes, rod outer segments) was studied in vitamin A deficient rats and pair-fed controls. The results suggest that the incorporation of glucosamine is increased in vitamin A deficiency. Although the function of vitamin A in the synthesis of proteins in the retina—and indeed in the body as a whole—is unknown, it was hypothesized that with vitamin A deficiency an abnormal glycoprotein is produced in excess. In the rod outer segments, where opsin is responsible for the structure of the outer segments, the abnormal protein apparently does not have the structural capabilities of opsin; hence, the well-documented histologic breakdown of the rod outer segments occurs.

### Fluorescein angiography in evaluation of diabetic retinopathy

Drs. P. Migasena and C. B. Mortimer (Toronto)—A numerical classification of changes seen on fluorescein angiography in this disease has been developed as an aid to evaluation. This method is used to compare findings in two groups of patients, both treated and untreated.

### The physiology of rod adaptation

Dr. M. Alpern (Ann Arbor)—To evaluate the role of pigment bleaching, rhodopsin kinetics in living human rods is investigated, using Stiles and Crawford's concept of the equivalent background of bleaching and its modus operandi, the automatic gain control model. Rushton's equation for foveal red and green cone pigment kinetics (with appropriate changes in constants) satisfactorily describes the kinetics of rhodopsin bleaching and regeneration over a fair range of experimental conditions. This allows a quantification of the amount of rhodopsin bleached by different exposure durations and intensities so that the relation between rhodopsin bleaching and threshold recovery can be analyzed within this range. Limitations of the general kinetics equation were discussed and the influences of bleaching and back-

grounds on psychophysical thresholds, pupil responses, and the á and b-waves of the ERG were analyzed.

### A CLINICAL TRIAL OF APPLANATION TONOGRAPHY

Drs. R. F. Stevenson and R. K. MacDonald (Toronto)—Applanation tonography was performed by a method wherein the corneal indentation is effected by an annular "thruster." When intraocular pressure readings are taken through the center of the thruster by the Goldmann applanation tonometer, and since this tonometer's movement is independent of the annular thruster, aberrations in ocular rigidity therefore do not influence the accuracy of the $P_0$ and $P_t$ readings. In the 22 normal and 18 hypertensive eyes analyzed, this method proved as reliable as regular tonography in assessment of aqueous flow, whether the pressure decrement quotient, or other method of assessment is used. This simple attachment to the biomicroscope will permit the clinician to perform the test in his own office.

### FREQUENCY SPECTRAL ANALYSIS OF THE DARK ADAPTED ELECTRORETINOGRAM

Drs. J. W. Waisberg and J. A. Parker (Toronto)—An electroretinography laboratory was set up and the equipment further adapted with an FM tape recorder for recording selected responses. Thirteen normal subjects were then tested and their responses recorded and statistically analyzed for four parameters (a-amplitude, b-latency, b-culmination, b-amplitude). Results showed no significant difference between the two eyes of normal subjects. A typical fully dark adapted ERG response was then presented to a set of active analogue filters and analyzed with respect to its wave-frequency content. This demonstrated that the basic ERG response is made up of low frequency waves (below 50 cps) and that the higher frequency components add the fine structure to the basic low frequency response.

### CHANGES OF LOWER EYELID APPOSITION PRESSURES WITH AGE

Drs. J. C. Walters and J. C. Hill (Toronto)—Looking for factors contributing to the development of senile entropion and ectropion, the "apposition pressure" of the lower eyelid on the globe was studied by placing two small fluid-filled balloons behind the lower eyelid, using topical anesthesia. One was placed behind pretarsal and the other behind preseptal orbicularis muscle fibers. These were connected to two pressure transducers and simultaneous tracings obtained, from which were taken the following readings: (1) resting pressure, (2) spontaneous blink-peak pressure, (3) reflex blink (only in some cases by glabella tap), (4) voluntary blink, and (5) squeeze. In the same individual variations were considerable. Between individuals, "pretarsal" and "preseptal" could be reversed, probably indicating unreliable anatomical relationships with the balloons. In the limited number studied no characteristic age pattern emerged.

### SCANNING ELECTRON MICROSCOPY OF THE TUNICA VASCULOSA LENTIS

Dr. M. J. Hollenberg and Mr. D. H. Dickson (London)—This instrument was used to study the vascular pattern and surface topography of the vessels forming the tunica vasculosa lentis in the fetal and neonatal rat in situ. On the final day of gestation, the vitreal surface of the lens was almost totally obscured by a rich, interwoven network of capillaries radiating from the central hyaloid vessel. On the corneal surface of the lens, a much less dense vascular pattern was formed by capillaries converging centrally from a series of short parallel vessels at the lens equator. During the first two weeks of neonatal life interconnecting capillary links disappeared on both lens surfaces, and the remaining main vessels became straighter and narrower. On the 16th day after birth, the only remaining capil-

laries, forming an incomplete, sparse, vascular tree, were on the vitreal lens surface.

THE PATHOPHYSIOLOGY OF NIGHT BLINDNESS

Dr. M. Alpern (Ann Arbor)—Some congenital abnormalities of the retina are characterized by poor night vision as revealed, for example, in defective rod dark adaptation. A small number of patients with abnormalities of this kind have been analyzed by psychophysical, electrophysiologic, and pupillographic tests, in addition to retinal densitometry, with a view to specifying the locus of the defects. The work so far permits a distinction to be drawn between defects of the rhodopsin system and defects of the automatic gain control. Furthermore, it allows a decision to be reached as to whether, in the normal subject, rhodopsin bleaching signals enter the automatic gain control through the input (according to Barlow) or through the feedback (according to Rushton).

COLOR VISION CAPABILITIES OF THE LEGALLY BLIND

Dr. P. K. Kaiser (Toronto)—Six legally blind subjects were tested for color vision by two procedures. Three of the subjects responded normally to the first, the HRR pseudoisochromatic color vision test. One subject was diagnosed as a mild protan, and the remaining two were unable to take the test. The second procedure involved having the subjects view three monochromatic lights at a 15-degree visual angle. The three who responded normally to the first test, as well as the one who responded as a mild protan to the HRR test, all responded normally on the color-naming task. The two remaining subjects gave clear indications of being able to correctly perceive colors towards the ends of the visible spectrum. This study suggests the possibility that colors near the end of the spectrum, reds or oranges and blues, might be used for color coding with the low vision population, but more important, this study demonstrates that a color-naming task would seem to be a more sensitive measure of color vision in persons with low vision than the standard color vision tests.

DISTURBANCES OF ROD THRESHOLD DUE TO TEMPOROSPATIAL PATTERNS OF BACKGROUND LIGHTING

Dr. P. E. Hallett (Toronto)—At the limits of rod vision a small subtense, brief duration signal can be detected if it excites a few retinal rods. The threshold energy of the signal must be increased if luminous backgrounds are present and if these show temporal or spatial changes in intensity, then there are also corresponding changes in the threshold energy of the superimposed signal. Analysis of such experiments involves signal/noise theory and spread functions and points to the importance of lateral inhibitory interactions at rod levels of illumination.

MICROTUBULAR DEGENERATION AND ALTERED GANGLION CELL ELECTRICAL ACTIVITY

Drs. D. R. Crapper and J. A. McLean (Toronto)—Colchicine is known to dissociate neuronal microtubules and block fast axonal transport in rabbit ganglion cell axons. Following 50 μg of intraocular colchicine, electronmicrographs show an increase in ganglion cell neuronal filaments and a decrease in microtubules. The optic tract photic-evoked electrical response progressively declines in amplitude following colchicine while the cortical response to electrical stimulation of the optic tract remains virtually unchanged when monitored by chronically implanted electrodes in unanesthetized rabbits. The ERG is not altered and supports the ultrastructural observation than the receptor, bipolar, and Müller cells are not affected by colchicine. The probable site of conduction failure is the postsynaptic membrane of the ganglion cell. These observations are in agreement with central nervous system observations that dendritic microtubular degeneration associated with neurofi-

brillary tangles is accompanied by a loss of synaptic receptor sensitivity.

LIGHT AND ELECTRON MICROSCOPIC RADIOAUTOGRAPHY OF TRITIATED GLUCOSE INCORPORATION IN THE RETINA OF THE ADULT NEWT

Mr. D. H. Dickson and Dr. M. J. Hollenberg (London)—When tritiated glucose was administered to fasted newts, incorporation of glucose into glycogen throughout the retina commenced at 30 minutes after injection. The first silver grain concentrations were observed over the photoreceptor myoid at two hours. Incorporation of glucose into glycogen reached a maximum at six hours, with grains concentrated over photoreceptor paraboloids, the apices of Müller cells and the inner and outer plexiform layers. By 24 hours there was a reduction of the label in glycogen, but silver grains were now visible over mitochondria in the photoreceptor ellipsoids and in increased amounts in the outer and inner plexiform layers and the nerve fiber layer. After three weeks, most radioactive material was observed over the photoreceptor cell outer segments.

INTERACTION BETWEEN NEAR ULTRAVIOLET LIGHT AND OCULAR PROTEINS

Dr. S. Zigman (Rochester)—A mechanism whereby the near ultraviolet (UV) portion of sunlight can alter physicochemical properties of ocular proteins after penetrating the cornea is suggested by in vitro experiments. Such light has been found to photooxidize aromatic amino acids and other aromatic substances (i.e., p-aminobenzoic acid) in buffers, physiologic solutions, and unaltered aqueous humor into colored compound which combine with lens and aqueous humor proteins.

Irradiation of tryptophan (5nm) in neutral aqueous buffers at 22°C for 24 hours with 3000 to 5000 $\mu w/cm^2$ of 340-380 nm light induced the formation of a yellow-brown oxidation product having twice the molecular weight of tryptophan, no free $\alpha$-amino groups, and altered absorption and fluorescence spectra. This product combined firmly with amino and sulfhydril groups of lens crystallins and many other proteins, coloring them, and appreciably altering their light absorption and fluorescence properties, their solubilities, and their electrophoretic mobilities. Human lenses incubated in physiologic media containing 5 mM tryptophan, and irradiated with near ultraviolet (UV) light as described above, became more intensely yellow-brown and absorbed blue light more efficiently. Uncolored rabbit lenses, irradiated for 72 hours in unaltered bovine aqueous humor also became yellow-brown as did the aqueous.

Our thesis is that aromatic compounds are photo-oxidized in the aqueous humor and lens by the near UV components of sunlight entering the eye. These substances combine with lens proteins leading to an increased browning with aging, and may result in brunescent cataracts. Other chemical changes in lens proteins, such as diminished solubility, may interfere with lens transparency. Alteration in the chemistry of aqueous humor proteins may result in the blockage of aqueous drainage channels, allergic manifestations, and altered eye tissue membrane permeabilities.

Practical application to eye health is suggested. Crystallin lens absorption protects the eye from harmful near UV energy, and aphakic persons should have near UV absorbing spectacles instead of ordinary optical glass. Xenon arc photocoagulators emit near UV energy potentially harmful to the aqueous humor and lens, suggesting a need for filtration of these wavelengths.

BIOSYNTHESIS OF PROTEINS BY THE RETINA

Dr. Y. Matuk (Toronto)—when the incorporation of $^{14}C$-leucine into TCA precipitable material from cell-free systems consisting of pH 5 fraction and pH 5 fraction-ribosomal preparations obtained from beef

retina was studied, optimum concentrations of ATP, phosphocreatine, $Mg^{++}$, and $K^{+}$ were determined. In every case concentrations of these substances that were higher than the optimum were inhibitory. Retinol and retinal had no effect on incorporation of $^{14}C$-leucine but puromycin and ethanol inhibited the incorporation. Inhibition by cycloheximide was found to be dependent on the concentration of pH 5 fraction used.

EXPERIMENTAL OCULOMYCOSIS

Mr. S. M. Hasany and Drs. J. J. Kazdan and P. K. Basu (Toronto)—To study the possible mechanisms by which opportunistic fungi may become harmful to the cornea, rabbit eyes were pretreated locally with corticosteroids (Depomedrol and Decadron) for 10 days prior to fungal spore inoculation into the cornea. In another experiment, fungi were cultivated in media containing corticosteroid (Decadron) and then extracts and filtrates of the fungi were prepared. These were inoculated into normal untreated rabbit corneas.

The result of the first experiment showed that the pretreatment of the external eye with corticosteroids enhanced the frequency and severity of corneal ulcer formation as compared to control eyes which were inoculated by an identical method, but not treated with corticosteroid. The result of the second experiment showed that the fungi had enhanced metabolic activity (increase of dry weight, increase of optical density of the media) when corticosteroid was added to the media, and also that extracts and filtrates prepared from these fungi were more harmful to the cornea as compared to those produced from fungi which were not cultivated in corticosteroid-containing media.

P. K. Basu

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## KRESGE EYE INSTITUTE ALUMNI 1971 CLINIC DAY PROGRAM

The 1971 Kresge Eye Institute Alumni Clinic Day program was presented at the David Whitney House, Wayne County Medical Society Auditorium, Detroit, Michigan, on Saturday, May 22, 1971.

Dr. Robert S. Jampel, Professor and Chairman of the Wayne State University Department of Ophthalmology, and Director of the Kresge Eye Institute, opened the program with a presentation of the floor plans and architectural drawings for the new Kresge Eye Institute Building, scheduled for completion in 1973. The new facility will provide space for basic research in the fields of pupillography, neurophysiology, biochemistry, and physiologic optics, as well as clinical facilities for electroretinography, ultrasonography, and fluorescein angiography. The pathology department will be expanded to three times its present size, and a large library and a lecture room for the basic science ophthalmology course is planned. In addition, there will be complete photography, contact lens, and prosthetic departments, along with clinical examining rooms provided for in the plans. The alumni were most appreciative of the effort put forth by Dr. Jampel to make the new facility an outstanding teaching center.

H. Saul Sugar reported on further developments in the use of deep lamellar resection of the cornea and sclera to remove epithelial cysts of the anterior chamber and ciliary body tumors. The final visual results were excellent, as were the clinical photographs.

William Sallee spoke on the advantages and disadvantages of soft contact lenses. Although the hydrophilic lenses are relatively easily tolerated, the disadvantages include maintaining continuous hydration, sterilization of the lenses, imperfect refraction correction, and limitation of astigmatic tolerance. The use of silicone or other "soft" gel materials may overcome these deficiencies.

Daniel T. Weidenthal presented his results in retinal detachment surgery. Reattachment was obtained in 90% of the cases. Approximately one-third of the cases obtained vision 20/50 or better; another third obtained vision of 20/50 to 20/200; and a third obtained only 20/200 or less. After successful reattachment surgery, there was a moderately good outlook as to treatment and final visual result of new holes.

Raymond R. Margherio spoke on the value of using an implant material (Gelfilm) in retinal detachment surgery. Because this material is absorbed gradually, there is less myopia following detachment surgery, and less likelihood of infection and extrusion of the implant.

Delbert P. Nachazel illustrated the use of radioactive $^{32}P$ in the diagnosis of intraocular masses. By exposing the sclera and performing selective counts in specific loci after an appropriate lapse of time, this test proved significantly valuable in differentiating hemorrhagic, inflammatory, and neoplastic lesions.

Ronald Goldman presented a series of orbital floor fractures corrected by the Caldawell-Luc approach. The use of maxillary antral packs was effective, and prevented the extrusion of orbital floor implants.

James A. Olson presented two cases of congenital anterior staphyloma, one bilateral. The corneas were grotesquely enlarged and bulged outwards through the palpebral fissures. Blindness was due to glaucoma following perforation of the cornea. Corneal infection, ulceration, and perforation appeared to be the dominant factor and congenital malformation of the anterior chamber angle was of secondary importance.

Craig W. George presented a case of a congenitally cystic globe. Repeated orbital surgery was required to eliminate the cystic mass during this patient's childhood; however, there was no direct communication of the cyst with the subarachnoid space.

Hugh Beckman discussed the use of lasers to perform iridectomies. After thorough testing in pigmented rabbits, the laser is now considered acceptable for clinical application in selected cases. The use of special intravenous dyes to concentrate specific wavelengths of laser light may aid in the use of laser surgery for lightly pigmented irides.

Ronald G. Agresta presented slides featuring the annual "smorgasbord" of interesting cases treated at Detroit General Hospital in the past year. This included a case of malignant melanoma with orbital extension and metastases to the breast in a young black woman, maxillary sinus carcinoma with a fulgating lesion the size of a fist which displaced the globe upwards and outwards, and the Meyer Schwickerath syndrome of bilateral microphthalmos and microcornea with bilateral acute congestive glaucoma.

Daniel R. Barr reported on the unusually high number of shotgun blast eye injuries seen at Detroit General Hospital. The clinical triad of hyphema, hypotonym, and chemosis usually indicates ocular perforation, and exploration of the orbit is indicated. The shotgun pellets may come to rest outside the globe; however, knowing the point of entry and the final resting place of the pellets enables the surgeon to plot their trajectory and determine whether the globe may have been perforated.

Henry Hirschman presented a three-year follow-up of 150 cataract operations using the intraocular iris-clip lenses. His success rate was high, and with the few complications encountered, this procedure may be more widely used in the near future.

Windsor S. Davies reported on the incidence of unsuspected uveal melanoma in evisceration contents submitted to the pathology laboratory. The ease of removing the scleral shell when malignant melanoma is found in evisceration contents lends support to the continued use of evisceration in indicated cases.

Michael Wainstock demonstrated the use of ultrasonography in the detection, localiza-

tion, and removal of intraocular foreign bodies, retinal detachment, intraocular masses and retrobulbar tumors.

Gerald T. Davies reported on the use of Dacron tape in frontalis sling operations. The material is easy to handle, stable, and ties well, causing little reaction at the knot site.

David Barsky reported on a fungus endophthalmitis occurring after perforation of a corneal ulcer. This elderly cardiac patient had undergone cataract surgery and had been maintained on topical antibiotic-corticosteroid drops for a long period. The need to suspect fungus infection in indolent corneal ulcers was emphasized.

The clinic ended following a brief business meeting and plans were made to schedule Saturday, May 20, 1972, for the next Alumni Clinic Day.

David Barsky

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OPHTHALMIC MINIATURE

Molenaer tended towards crowded scenes, while his early warm, clear colors gave way to overall brown tones. Perhaps in Molenaer's case—as in the case of Degas, whose bright palette gradually changed towards a predominance of monotonous reds and browns as he grew older—this evolution in coloring was due to slowly developing cataracts, a theory that has been convincingly suggested by the London ophthalmologist and art connoisseur, Patrick Trevor-Roper.

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## THE SECTION IS DEAD. LONG LIVE THE SECTION COUNCIL!

Many individuals within and without the AMA have been predicting the demise of the Section on Ophthalmology. However, the 91-year-old "adult" was alive and well at the recent meeting in Atlantic City. Over 250 guests registered attendance during the two-day scientific program. Algernon B. Reese, Distinguished American Guest, spoke on pigmented lesions in and about the eye as culled from his vast personal experience. Hans-Walther Larsen, Distinguished Foreign Guest, discussed angioid streaks in patients with and without pseudoxanthoma elasticum as studied in a series of patients that he has been following in Copenhagen. A highlight of the meeting was a symposium on the management of common uveitis syndromes chaired by David L. Knox of Baltimore.

In addition, 21 short presentations were offered. These covered the spectrum of medical and surgical aspects of clinical ophthalmology. As seen and heard from the podium it is difficult (and dangerous) to select those papers which stood above the others, but from a biased standpoint a few come to mind.

Electric cataracts described by Hanna and Fraunfelder was an electrifying presentation. Aphakic pupillary block treated with vitriotomy by Cotlier and Herman and discussed by Scheie provided food for thought. A young ophthalmologist, Guggino, a masterful discussion of the home measurement of intraocular pressure. This evoked much discussion from the audience, one of the unique features of the AMA meeting. Best and Galin made careful clinical studies of fluorescein angiography in glaucomatous patients using suction-cup ophthalmodynamometry. Levene of New York City and Rieser and Schwartz of Boston provided new insight into the problem of malignant glaucoma. The surgical treatment of eyelid retraction was well presented by Putterman and Urist. Solar retinopathy resulting from sun gazing while under the influence of LSD stimulated considerable comment. In the discussion it was noted that the sun cannot produce a photocoagulation burn, which was news to some of us.

In order to prove that ophthalmology is not unrelated to general medicine Christensen and Pettit discussed optic nerve involvement in ulcerative colitis. Roth and Foos likewise presented a superb study of eye findings in hemochromatosis, and their paper was selected as the most deserving of the Knapp Fund award for 1971.

Ten ophthalmic exhibits were of high caliber. Televised fluorescein angiography in the human fundus by Van Heuven, Schaffer, and Mehu of Albany was selected for the Knapp award. This method bids fair to add a new dimension to angiography, since the light input is minimal and analyses can be made instantaneously.

In keeping with the dictates of the AMA at large, the 91-year-old Section on Ophthalmology passes out of existence at the end of the current year. It will be replaced with a new Section Council consisting of representatives from the various large ophthalmic societies. Chosen to lead this new venture is Bernard Becker, as chairman, and Joseph M. Dixon, as vice-chairman. Falls and Jaeckle will continue to represent ophthalmic interests in the AMA House of Delegates as Delegate and Alternate Delegate, respectively. Davis will continue as representative for exhibits and Duane will serve as secretary and representative for programs.

The Section is dead. Long live the Section Council!

Thomas Duane

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## THE INTERNATIONAL EYE FOUNDATION

### A Decade of Progress*

In 1960, the late Doctor Thomas A. Dooley, who had committed his brief life's work to the developing countries of Southeast Asia, discussed with me the need for more and better eye surgical care among his patients. He particularly emphasized the large number of blind persons suffering from corneal scarring or disease. Tom was told that efforts would be made to organize trained eye surgeons to survey these areas with a view to attempting to offer some help.

On Tom Dooley's last trip to the Orient, he was hospitalized in Hong Kong for a back ailment which later proved to be metastatic melanoma. Upon his return to the United States, he stated that he had promised the ophthalmologists there that a team would be forthcoming to aid them in establishing an eye bank and in learning the techniques of cornea grafting. In early 1961, the International Eye Bank (IEB) was formed, and ironically, Tom Dooley's eyes were among the first to be donated to the bank. He died on January 18, 1961.

The IEB was organized as a facet of Medico, Dooley's dream, and the medical arm of Care. Donor eye tissues were shipped to other countries where they were des-

*Abstracted by the author from his presentation before members and guests attending the Foresight luncheon during the First Congress of the Society of Eye Surgeons, Washington, D.C., May 27, 1971.

perately needed but were not available because of religion, custom, or law.

At the request of the Hong Kong Ophthalmological Society, a team of three ophthalmic surgeons (the late John M. McLean, Charles E. Iliff, and I) went to the British Crown Colony in the Fall of 1961. The number of blind persons in Hong Kong was large—greatly disproportionate to the total population. Many of these were refugees who had been "dumped" by Communist China. A large number suffered from curable corneal blindness. The local eye surgeons were well trained, but had little knowledge of grafting because of a total lack of donor materials. The first teaching mission was successful beyond every expectation—35 demonstration operations were performed, and the Chinese ophthalmologists organized an effective eye bank.

Fresh donor eyes and glycerine-preserved corneas were sent by air to numerous countries, and more teaching teams were requested. It became obvious that eye tissues alone were not the answer—teaching in all aspects of ophthalmic surgery was desired. Voluntary teams were sent to many countries, and an 80-bed eye unit was established in Algiers, manned by Johns Hopkins University. Virtually every area of the world was visited by a volunteer or a team, and assistance was given in forming eye banks where requested.

In 1965, the International Eye Bank became a branch of the IEF, and in maintaining its primary purpose of teaching, the functions of the IEF, were expanded far beyond corneal surgery. By 1968, the IEF had outgrown the financial support available from CARE-MEDICO and reluctantly left this organization to become an independent foundation. It adopted the slogan, "The promotion of peace through the prevention and cure of blindness worldwide." Perhaps this was an exaggerated ambition, but it provided challenge to ophthalmologists of the "have" nations to help those in the developing and "have not" nations. The IEF was not designed as a missionary effort, however, and it continued to offer a self-help, people-to-people program with every effort geared to teaching. Each program was time-limited, planned as a cooperative mission with the host country, and intended to be terminated when a developing nation became self-sufficient with trained ophthalmologists.

Exchange fellowships were established with the donations of generous laymen, and the Bunker, Carrigan, Clagett and Hermann fellowships became well known. Funds were raised through social affairs; private foundations were established, several industries associated with ophthalmology gave generously, as did many individual ophthalmologists who became members of the IEF's Foresight Club. Programs were expanded as more funds were forthcoming, but within a very few years, we found we had a "tiger by the tail"—only a small number of the many requests could be implemented.

The sponsorships of ophthalmologists volunteering their services and the support of the Eye Bank Association of America made the IEF a progressive teaching organization, attempting to fulfill an urgent need in international ophthalmology, concentrating upon clinical aspects.

During the past 10 years, 323 fellowships have been sponsored—170 from this country and 153 from other countries. These are short-term, limited to a maximum of six months. Junior fellowships are offered to ophthalmology residents in their last three months of formal training and senior fellowships are granted to those who have completed residencies.

At six universities or large government hospitals in other countries, units have been established in which fellows from the United States are rotated, while the young ophthalmologists from other countries are sponsored for short-term general or sub-specialty ophthalmic training in the United States. Student ophthalmologists from other countries are selected by the ophthalmic Societies in their homelands to be given training in

facets of ophthalmology sometimes lacking in their own teaching hospitals. An increasing number of young ophthalmologists in this country are requesting these assignments abroad in order to obtain more surgical experience, especially since the advent of Medicare and Medicaid, which has seriously reduced surgical training in some areas of the United States. In addition, these volunteers have the satisfaction of knowing they have added "pair of hands" to reach some of the curable blind in a country where there are too few ophthalmologists and too many persons without sight. While our young men serve in institutions abroad, they are responsible to the Director of the Department of Ophthalmology, a highly trained and capable individual dedicated to teaching.

The International Eye Bank has shipped over 6000 corneas to 55 countries during the past decade. These have come from virtually every eye bank in the United States. In addition, this most important branch of IEF has assisted in the establishment of 29 eye banks in 26 countries.

Visiting full-time professors are sponsored for teaching tours abroad. Visiting surgeons, in private practice and with clinical teaching posts at universities, are partly sponsored, usually for longer tours.

The Pan American Association of Ophthalmology has sponsored 30 fellows from 13 Latin American countries to the excellent basic science courses given in Spanish at the University of Puerto Rico. They return home to complete training and then to treat their own people.

The urgent need for teaching units in countries such as Indonesia, where there are many blind persons, has been partly answered by a small grant from USAID, pinpointed to certain areas.

A much-needed, new and exciting program has recently been established. Short courses are being instituted for the training of ophthalmic assistants in Indonesia and in Pakistan. As a result of this program, the few ophthalmologists now practicing in these countries will be able to examine and treat more patients; thus, their skills will be directed where they are most needed. A full-time ophthalmic technician on the IEF staff is in charge of these programs. United States-trained technicians have volunteered to assist with courses on short-term tours.

The Society of Eye Surgeon (SES), established in 1969 as the medical facet of the IEF, has given much impetus to IEF's progress. A report of its first meeting is given elsewhere in this journal. Its membership is worldwide. Funds derived from the SES are applied solely to the support of exchange fellowships and to units abroad—none are used for administration.

The IEF is a unique organization—a small, public foundation, non-sectarian and non-governmental, volunteering its abilities to upgrade eye surgical care throughout the world. Established ophthalmologists give their services, and at the same time donate money, to sponsor young ophthalmologists who need further surgical training and experience. This is a "two-way road"; it is not only a humanitarian effort by our specialty, it also makes ophthalmology a potent worldwide diplomatic force.

We are deeply involved in teaching and in trying to help others. The IEF has become well known and highly respected over the past 10 years. With the continued assistance of our lay donors and ophthalmologists of all nations, it will do more during the next decade.

The supporters of the International Eye Foundation could well have written these words of Louis Pasteur, a scientist dedicated to helping the unfortunate of all nations: "One does not ask of one who suffers, 'What is your country and what is your religion?' One merely says, you suffer; this is enough for me. You belong to me and I shall help you."

J. H. King, Jr.
*Washington, D.C.*

## CORRESPONDENCE

### Eye pad flammability

Editor,
American Journal of Ophthalmology:

Authors Weiss and Skalka recently reported the dangerous flammability of eye pads (Am. J. Ophth. 71:1344, 1971). I would like to re-emphasize their concern. A 48-year-old patient, on whom I had performed an uneventful cataract extraction five weeks previously, called to say that 10 hours earlier this eye pad covering his operated eye had caught on fire while he was attempting to light a cigarette over a gas stove. He sustained second and third degree burns of the face and eyelids with tremendous swelling of the eyelids. Fortunately, the eye itself was not injured, and the burns responded to antibiotics and compresses applied in the hospital. Several weeks later his eye was back to normal, with 20/30 corrected vision.

We should caution smokers, especially those who we know to combine this with heavy alcoholic intake, as to this potential danger.

Frank J. Weinstock
*Canton, Ohio*

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### Transpupillary cyclophotocoagulation

Editor,
American Journal of Ophthalmology:

In Figures 3, 4, 8, and 9 of the article entitled "Transpupillary cyclophotocoagulation of rabbit eye," by myself and Oleg Pomerantzeff (Am. J. Ophth. 71:911, 1971), the structure labeled *cb* is the iris and the structure labeled *s* is corneal stroma. In Figures 3 and 4, the iris and ciliary body were displaced toward the cornea, while in Figures 7 and 9, the sections were equatorial and the calotte cut unevenly so that some corneal tissue remained. I regret the inconvenience caused by this error.

Pei-Fei Lee
*Boston, Massachusetts*

## BOOK REVIEWS

Ultrastructure of the Peripheral Nervous System and Sense Organs. Atlas of Normal and Pathologic Anatomy. By Jean Babel, Albert Bischoff, and Heinrich Spoendlin. St. Louis, C. V. Mosby, 1970. Clothbound, 452 pages, table of contents, index, 203 black and white figures. $45.25.

This is an atlas of electron microscopic pictures concerned with the peripheral nerve, the auditory, vestibular, olfactory, and gustatory organs, as well as the retina.

The first part is written by Bischoff, a neurologist in Zurich. He covers especially the normal anatomy and the general pathology of peripheral nerves. This is a most instructive introduction to the ultrastructure of these organs and the coverage seems to be quite complete. In the chapter on special pathology, Bischoff concerns himself mainly with metabolic diseases affecting the peripheral nerve. The chapter on motor end plate is illuminating.

The second part of the book deals with various sensory end organs and is by Spoendlin, an otolaryngologist in Zurich.

Ophthalmologists will be mainly interested in the third part of this book which is concerned with the retina. It is written by J. Babel, professor of ophthalmology at Geneva. Dr. Babel discusses the normal anatomy of the retina first and illustrates it mainly with specimens from the rabbit which are fixed much more quickly than human material. The pathologic considerations of the retina center around toxic damage to this organ; damage produced by monoiodacetate, sodium iodate, chloroquine, and iron are especially well covered. The presentation is lucid and instructive.

The pictures are of superb quality and reproduced in an exemplary manner. It is indeed an esthetic pleasure to look at this book and study it. The accompanying text is short, but to the point. The references are most helpful.

F. C. Blodi

# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ANNALES D'OCULISTIQUE

INTOLERANCE TO SILICONE SPONGES IN SURGERY OF DETACHMENT OF THE RETINA. (French) Rouchy, J. P. (11, avenue Elisee-Reclus, Paris-7e), Ann. Ocul. 204: 55-65, Jan., 1971.

There were no infections in 140 cases in which silicone sponges were used as either implants or explants for retinal detachment surgery. However, nine caused irritation severe enough to require removal. In none of these cases did a retinal detachment follow.—David Shoch

## ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

THE FINE STRUCTURE OF THE SO-CALLED OUTER LIMITING MEMBRANE IN THE HUMAN RETINA. (German) Spitznas, M. (Dept. Ophth. Univ. of Cal., San Francisco, Cal. 94122), Arch. Klin. Exp. Ophth. 180:44-56, 1970.

The outer limiting membrane is not a true membrane but appears under the electron microscope as a layer of intracellular, cytoplasmic densities which should be considered as zonulae adhaerentes. The latter are a special type of intracellular junction which have primarily a mechanical function. (8 figures, 22 references)—Walter Segall

PRACTICAL SIGNIFICANCE OF THE PROVOCATIVE TESTS IN GLAUCOMA. (German) Makabe, R. (Univ. Augenklinik, D-6000 Frankfurt a.M., Germany), Arch. Klin. Exp. Ophth. 180:193-203, 1970.

At least three of the five provocative tests (Priscol, water drinking, darkroom, mydriasis and caffeine test) were performed in 100 eyes with incipient simple glaucoma. The results of these tests showed significant positive relationship to simple tonometry and diurnal variations of intraocular pressure. (10 tables, 15 references)—Walter Segall

THE IMPROVED EVALUATION OF PROVOCATIVE TESTS IN GLAUCOMA. (German) Makabe, R. (Univ. Augenklinik, D-6000 Frankfurt a.M., Germany), Arch. Klin. Exp. Ophth. 180:204-210, 1970.

In 231 patients with incipient chronic simple glaucoma three out of five provocative tests (darkroom, mydriasis, caffeine, Priscol and water drinking) were performed. The percentage of pathologic results is as follows: water drinking test 52.5%, Priscol test 48.2%, mydriasis, darkroom and caffeine test 20.0% (3 figures, 16 references)—Walter Segall

COMPARISON OF THE PROVOCATIVE TESTS FOR GLAUCOMA WITH EACH OTHER. (German) Makabe, R. (Univ. Augenklinik, D-6000 Frankfurt, Germany), Arch. Klin. Exp. Ophth. 180:211-216, 1970.

In 231 patients with incipient chronic simple glaucoma three out of five provocative tests were performed (Priscol, water drinking, mydriasis, darkroom and caffeine test). There was no significant relationship between the results of the water drinking test and the Priscol test. However, the results of the Priscol test showed relationship to those of caffeine, the darkroom and the mydriasis test; there was also a significant relationship between mydriasis and darkroom test. (1 table, 18 references)—Walter Segall

ELECTRON MICROSCOPIC STUDIES OF THE CHANGES DUE TO AGE IN THE ZONULA ZINNII OF THE HUMAN EYE. (German) Gaertner, J. (Univ. Augenklinik, D-6500 Mainz, Germany), Arch. Klin. Exp. Ophth. 180:217-230, 1970.

Eight human eyes were studied from patients 9 months to 78 years old. The fibrils and the cement substance of the zonular fibers are produced by fibroblasts located in the region of the Zonula Zinnii especially close to the pars plana. The cilio-zonular basement membrane consists of one layer in juveniles; in adults it forms a multilayered meshwork with granular and lamellar deposits, probably lipids. With increasing age the zonular fibril bundles

show degenerative changes. (7 figures, 23 references)—Walter Segall

VASCULITIS OF THE MARGINAL ZONE OF THE RETINA. (German) Slezak, H. (Augenklinik der Universitat Wien), Arch. Klin. Exp. Ophth. 180:267-272, 1970.

Sometimes sheathed vessels can be seen in the periphery of the retina in eyes with dust-like opacities of the vitreous body; it can be differentiated from peripheral uveitis and from the peripheral form of Eale's disease by biomicroscopic examination and fluorescein angiography. (6 figures, 14 references)—Author's abstract

STUDIES ON THE ALTERED ETIOLOGY OF HYPOPYON ULCER. (German) Bock, J. and Flamm, H. (Augenklinik und Hygiene-Institut), Arch. Klin. Exp. Ophth. 180: 299-316, 1970.

As Ps. pyocyanea and Staph. aureus become more resistant to antibiotics, these germs seem to replace the previously dominant Pneumococcus as the main cause for hypopyon ulcer of the cornea. The cause of this shift seems to lay not only in the propagation of these germs by air humidifiers, contaminated eye-drops, contact lenses etc., but also by the widespread use of antibiotics in ophthalmology. Experimental results show that the primary resistance of the rabbit cornea against Ps. pyocyanea can be reduced by local application of chloromycetin drops. This fact should warn ophthalmologists to reduce the often unnecessary and uncontrolled use of antibiotics as much as possible. (2 tables, 117 references)—Authors' abstract

EXAMINATIONS OF TENSILE STRENGTH OF GLUE AND SUTURED ISOLATED CORNEOSCLERAL STRIPS. (German) Giessmann, H. G., Schlote, H. W., Tuchscherer, V. and Zeller, R. (Augenklinik der Medizinischen Akademie Magdeburg), Arch. Klin. Exp. Ophth. 181:17-24, 1970.

The tensile strength of 10 mm wide corneoscleral strips from cow-eyes was measured using sutures and glue wounds. Glued strips showed at least an equal tensile strength to sutured ones, and in several cases it was significantly higher. (10 figures, 1 table, 16 references)—Authors' abstract

## ARCHIVES D'OPHTALMOLOGIE

CONCERNING 17 CASES OF RETINAL DETACHMENT IN CHILDREN. (French) Farnarier, G. and Alessi, F. (C.H.U., Hopital Nord, 13-Marseilles, XV$^{e}$, France), Arch. Ophtal. 30:277-290, Apr., 1970.

Cases reported stress the frequency of trauma as the etiology, with poor prognosis in high myopia and with prolonged duration of detachment. (3 tables)—Maurice Kadin

ROLE OF THE CORNEA AND LENS IN BIOMETRY OF THE NORMAL ANTERIOR CHAMBER. (French) Delmarcelle, Y., Collignon-Brach, J. and Luyckx-Bacus, J. (Clinique ophtalmologique, Hopital de Baviere, 66, boulevard de la Constitution, Liege, France), Arch. Ophtal. 30:291-300, Apr., 1970.

Utilizing optical biometry and ultrasonography, the authors studied the influence of the cornea and lens on the anterior chamber depth. The anterior depth of the anterior chamber depends on corneal radius of curvature, diameter, thickness and peripheral flattening. The posterior portion depends on the position of the lens insertion and its thickness, and can be measured by ultrasonography. This is the most variable factor, and determines the degree of the opening of the chamber angle. (5 figures, 1 table, 9 references)—Maurice Kadin

PHOTOCOAGULATION OF ANGIOID AFTER FLUORESCEIN ANGIOGRAPHY. (French) Offret, G., Coscas, G. and Orsoni-Dupont, C. (16, rue Logelbach, Paris (XVIIe), France), Arch. Ophtal. 30:419-422, May, 1970.

The authors present two cases in which photocoagulation of angioid streaks was done following fluorescein angiography with the object of preventing extension into the macular area and chorioretinal hemorrhages. (4 figures)—Maurice Kadin

CHROMATIC VISUAL DISTURBANCES IN CENTRAL SEROUS CHORIORETINOPATHY. (French) Coscas, G. and Legras, M. (192 bis, rue de Vaugirard, 75-Paris, XV$^{e}$, France), Arch. Ophtal. 30:491-496, June-July, 1970.

Disturbances of color vision, usually yellow-blue dyschromatopsia, occur in central serous retinopathy before visual loss. (1 figure, 1 table, 15 references)—Maurice Kadin

REFSUM'S DISEASE. (French) Rougier, J. (4, rue de la Charite, 69-Lyon (2e), Arch. Ophtal. 30:665-672, Oct., 1970.

Refsum's disease described in 1945 comprises a neurological syndrome with chronic polyneuritis and cerebellar ataxia, an ophthalmological syndrome with hemeralopia, a shrinking of the field of vision and atypical pigmentary retinitis and a biological syndrome consisting in the presence of phytanic acid in serum. The author reports on the observation of a family in which the father and the mother present no lesions. Elder brother and sister present a complete Refsum's disease and the younger brother has only modifications of the adaptometric curve. The last child shows no clinical or biological signs. (5 figures, 8 references)—Author's abstract

CAN RETINOPATHY BE PREVENTED BY A MORE PHYSIOLOGICAL TREATMENT OF DIABETES? (French) Tutin, M., Tchobroutsky, G. and Guyot-Argenton, C. (7 bis, rue Lesueur, Paris (XVIe), Arch. Ophtal. 30:697-700, Oct., 1970.

In all aspects of diabetes mellitus there exists an inadequate insulin secretion which explains the development of retinopathy. Therapy should aim towards a closer approximation to physiological conditions and multiple insulin injections are proposed. (4 references)—Authors' abstract

HYPERLIPIDEMIA AND DIABETIC RETINOPATHY. (French) Moreau, P. G. and Pichon P. (10, boulevard de la Trémouille, 21-Dijon), Arch. Ophtal. 30:757-768, Nov., 1970.

After a surgey of the different lipids of the body we can understand the five groups of hyperlipidemia described by Fredrickson. We have summarized by easier and most valuable laboratory analyses. Hyperlipidemic retinopathy in fact is frequent and proofs are statistical and experimental; the ophthalmoscopic disorders are described and are correlated with the five groups of hyperlipidemia of Fredrickson. Consequently diabetic retinopathy appears like a kind of hyperlipidemic retinopathy and some arguments verified this proposal. Triglycerides seem to be of great importance in the disease. (10 figures, 16 references)—Authors' abstract

ULTRASTRUCTURAL STUDY OF CORNEAL THICKENING IN THE COURSE OF CHLORPROMAZINE TREATMENT. (French) Pouliquen, Y., Graf, B., Bisson, J., Feuvrier, Y.-M. and Delattre, A. (22, rue Henri-Heine, 75-Paris (XVIe), Arch. Ophtal. 30:769-782, Nov., 1970.

A fragment of the cornea of a patient with corneal thickening due to phenothiazine was examined under electron microscope. A stimulation of melanogenesis at the level of the epithelium and a diffuse excess of anterior stroma due to the drug or its metabolites were observed. The keratocytes react phagocytically to this thickening. (16 figures, 5 references)—Authors' abstract

PROSTAGLANDINS IN OPHTHALMOLOGY. (French) Demailly, P., Saindelle, J. and Saindelle, A. (71, avenue Kleber, 75-Paris (XVIe), Arch. Ophtal. 31:53-62, Jan., 1971.

Prostaglandins E and R have been isolated by chromatographic methods from the iris of various species. This tissue is also able to synthetize prostaglandin in vitro. Injected into anterior chamber of the eye, prostaglandin induces a long-lasting miosis, which is not modified by atropine. (7 figures, 21 references)—Authors' abstract

OPHTHALMIC HERPES ZOSTER: ISOLATION OF A VIRUS STRAIN FROM THE AQUEOUS HUMOR. (French) Denis-Lassalle, J., Clay, C., Cherardi-Bakalova, M. and Offret, G. (Hotel-Dieu, place du Parvis Notre-Dame, Paris), Arch. Ophtal. 31:109-118, Feb., 1971.

A patient had severe ophthalmic herpes zoster and at the end of the second month of the disease a virus was isolated from the aqueous. This may account for the associated uveal inflammation seen in this disease. The characteristic histologic lesion appears to be leukocytic infiltration around ciliary vessels and nerves similar to that seen in a hypersensitiv-

ity phenomenon. (1 figure, 39 references)—David Shoch

THE ELECTRO-OCULOGRAM. (French) Dorne, P. A. and Espiard, J. F. (Lyon, France), Arch. Ophtal. 31:217-224, Mar., 1971.

The most interesting use of the electro-oculogram is the fact that its extinction is pathognomonic of vitelliform degeneration of the macula. It helps to confirm this diagnosis at any ophthalmoscopic stage and also helps to find gene carriers with normal fundi. (4 figures, 1 table, 5 references)—David Shoch

A CLINICAL STUDY OF COLOR SENSE DISTURBANCES DURING OPACIFICATION OF THE CRYSTALLIN LENS AND AFTER CATARACT EXTRACTION. (French) Karantinos, D. (26, rue de l'Universite, Athens, Greece), Arch. Ophtal. 31:235-244, Mar., 1971.

Color sense disturbances begin as soon as the opacification of the lens starts and discrimination becomes worse as the cataract progresses. Postoperatively there is a great color sense disturbance for the first few days after the operation. Six months later most of the cases have a normal color sense. Cyanopsia and erythropsia were observed in a few patients. The Farnsworth 100-Hue test gives the most reliable results and the Ishihara pseudoisochromatic plates the least reliable. (2 figures, 5 tables, 32 references)—David Shoch

DIABETIC RETINOPATHY. (French) Adle, E. H. and Samii, F. (293, avenue Takte-Jamshid, Teheran, Iran), Arch. Ophtal. 31:259-262, Mar., 1971.

In the authors' series of 100 patients with diabetic retinopathy a very strict control of the diabetic state with diet and insulin resulted in an improvement in the retinal changes. Recurrences were observed when diabetic control was lost. The addition of anabolic steroids, Vitamin C, P, and K did not improve the results. (1 table, 2 references)—David Shoch

## ARCHIVES OF OPHTHALMOLOGY

KERATOMYCOSIS. Polack, F. M., Kaufman, H. E. and Newmark, E. (College of Medicine, University of Florida, Gainesville, Florida), Arch. Ophth. 85:410-416, Apr., 1971.

Since the increased use of topical steroids there has been a parallel increase in the incidence of corneal mycotic infections. The authors discuss a series of 33 patients, in 17 of whom there was a previous history of injury with vegetable matter. Eight of the patients had been treated with steroids and antibiotics. Twenty-two of the patients required surgical procedures to control the infection. This included keratectomies, conjunctival flaps and penetrating keratoplasties. (9 figures, 2 tables, 19 references)—David Shoch

PSEUDOPAPILLEDEMA OF JUVENILE DIABETES MELLITUS. Lubow, M. and Makley, Jr., T. A. (Ohio State University Hospitals, Means Hall 25, Columbus, Ohio 43210), Arch. Ophth. 85:417-422, Apr., 1971.

Optic disc edema with neovascularization, peripapillary hemorrhages, and exudates mimicking true papilledema occurred in three teenaged patients with long-standing juvenile diabetes mellitus controlled by insulin. Despite the appearance of papilledema, the unusual signs, symptoms, and course of this syndrome suggest that it is an ischemic manifestation of diabetic microangiopathy within the optic papilla in the absence of adequate collateral circulation. This report confirms the existence of a diabetic optic neuropathy, and discusses its vascular pathogenesis and management. (13 figures, 11 references)—Authors' abstract

INTRAOCULAR PRESSURE IN DIABETES. Bouzas, A. G., Gragoudas, E. S., Balodimos, M. C., Brinegar, C. H. and Aiello, L. M. (59 Skoufa, Athens 135 Greece), Arch. Ophth. 85:423-427, Apr., 1971.

The intraocular pressure of 101 unselected diabetics was correlated to the presence of retinopathy, the blood glucose level, and various clinical factors. The following conclusions were drawn: (1) The mean intraocular pressure in unselected diabetics is not different from that of the general population. There is no difference in mean pressure between juvenile and maturity-onset diabetics. (2) Sex, present age, duration of diabetes, blood pressure, blood glucose level, and type of antidiabetic therapy showed no relation to the intraocular pressure. (3) The presence or absence of retinopathy was not related to the intraocular pressure in these patients with pressures still within normal limits. These essentially

negative results support several earlier studies. They differ from some reports originating mainly from ophthalmological clinics, in which differences have been reported. (2 figures, 2 tables, 35 references)—Authors' abstract

MEDRYSONE HYPERSENSITIVITY. Smolin, G. (Francis I. Proctor Foundation, University of California, San Francisco Medical Center, San Francisco 94112), Arch. Ophth. 85:478-479, Apr. 1971.

A patient treated for an inflamed pinguecula with 1% medrysone (HMS) developed a typical delayed hypersensitivity reaction. This was established as a reaction to the medrysone rather than to any of the substances in the vehicle. (6 references)—Author's abstract

## BRAIN

ACQUIRED LESIONS OF THE FOURTH CRANIAL NERVE. Burger, L. J., Kalvin, N. H. and Smith, J. L. (Department of Ophthalmology, University of Miami School of Medicine, Miami, Florida), Brain 93:567-574, 1970.

Thirty-three cases were included in this study of isolated acquired fourth nerve palsy. The three commonest causes were injury, vascular disease, and diabetes. The subjective red glass Bielschowsky test and observation of the patient's head posture are simple methods for diagnosis of superior oblique weakness. (14 references)—Joel G. Sacks

## BRITISH JOURNAL OF OPHTHALMOLOGY

KERATINOID CORNEAL DEGENERATION. Garner, A. (Institute of Ophthalmology, Judd Street, London, England), Brit. J. Ophth. 54:769-780, Dec., 1970.

Globular hyaline deposits in the superficial stroma and epithelium of the cornea have been recognized under a variety of names for many years. Sometimes seen as an isolated phenomenon, they are usually observed in association with other corneal disorders, and the present report is concerned with their occurrence in three cases of lattice dystrophy, one of subepithelial corneal fibrosis, and one of post-traumatic scarring . . . . Histochemical analysis indicates that the deposits are composed essentially of protein and suggest that they may be related to keratin, possibly as a precursor or incomplete form. In the absence of an existing satisfactory terminology, it is proposed that the process wherein the sulphur-rich globular deposits are formed be referred to as keratinoid corneal degeneration. The multiplicity of the corneal disorders in which the abnormal material is formed implies that the keratinoid deposits do not constitute a separate disease entity so much as a special type of response which may be stimulated in a variety of ways. (15 figures, 1 table, 27 references)—Author's abstract

PARTIAL EVULSION OF OPTIC NERVE. Hart, J. C. D. and Pilley, S. F. J. (Western Ophthalmic Hospital, London), Brit. J. Ophth. 54:781-785, Dec., 1970.

A case of partial evulsion of the optic nerve is presented in which fluorescein angiography was performed. The study demonstrated that, in spite of the extensive nature of the injury, the major retinal vessels were minimally affected with transit of dye through both arteries and veins. The only vessels significantly affected were small vessels in the region of the disc. The field loss was due to rupture of nerve axons at the margin of the disc. (4 figures, 9 references)—Authors' abstract

INTRAOCULAR PRESSURE REDUCTION AND VITREOUS MASS. Robbins, R., Obstbaum, A. S., Best, M. and Galin, M. A. (New York Medical College, New York), Brit. J. Ophth. 54:801-804, Dec., 1970.

Retrobulbar anesthesia and the use of acetozolamide reduce intraocular pressure in the undisturbed rabbit eye, but do not alter vitreous weight. The former technique may be beneficial in lens extraction procedures in that it counteracts the mechanical forces which tend to extrude vitreous. The use of acetazolamide is of no value in preventing vitreous loss. (3 tables, 8 references)—Authors' abstract

FLAT ANTERIOR CHAMBER AND CHOROIDAL DETACHMENT IN APHAKIA. Shah, R. R. (Rajkot, Gujarat, India), Brit. J. Ophth. 55:48-49, Jan., 1971.

In 500 cases of cataract extraction the incidence of choroidal detachment was 2.6% and that of shallow anterior chamber was 13.5%, and there was no regular relationship between

the two conditions. The eyes were treated conservatively and these complications did not affect the ultimate visual acuity or intraocular pressure. (4 references)—Author's abstract

ISCHEMIC OPTIC NEUROPATHY IN CHRONIC SIMPLE GLAUCOMA. Begg, I. S., Drance, S. M. and Sweeney, V. P. (Department of Ophthalmology, 2550 Willow Street, Vancouver, Canada), Brit. J. Ophth. 55: 73-90, Feb., 1971.

The occurrence of discrete, recurrent, and sometimes bilateral hemorrhages in sectors of the disc, in the region of the arcuate nerve fibers, associated with fresh absolute field defects in the Bjerrum area was thought to characterize symptomless ischemic optic neuropathy. These changes were observed in three patients with ocular hypertension, marking the transition to chronic simple glaucoma. A similar sequence marked the progression of field loss in four patients with chronic simple glaucoma. The general neurovascular assessment of the patients, their level of intraocular pressure at the time of the field loss, and the ophthalmodynamometric findings suggested that the ischemic optic neuropathy in this group of patients was probably due to small vessel disease, producing inadequate perfusion of the optic nerve head. Adverse perfusion pressures were seen in only some of this group of patients, which suggests that there are many causes for poor perfusion at the optic nerve head. An imbalance between intraocular pressure and vascular pressure, while common, is not the only cause of a nerve fiber bundle infarction indistinguishable from that found in chronic simple glaucoma. (1 table, 18 figures, 22 references)—Authors' abstract

EXPERIMENTAL OCULAR SCHISTOSOMIASIS. Abboud, I. A., Hanna, L. S. and Ragab, H. A. A. (Cairo University, Egypt), Brit. J. Ophth. 55:106-115, Feb., 1971.

The injection of suspensions of cercariae subconjunctivally in animals did not cause ocular lesions, but produced generalized schistosomiasis. The instillation of cercariae on to the eyelids and conjunctiva also produced generalized schistosomiasis. Injection of cercariae into the anterior chamber of guinea-pigs resulted in an aqueous flare, keratic precipitates, and hypopyon, but generalized schistosomiasis did not develop. The eyes of animals previously infected with cercariae of S. mansoni through the intraperitoneal route revealed no ocular lesions. The eyes of 150 patients suffering from schistosomiasis showed subconjunctival hemorrhages in twelve and flame-shaped retinal hemorrhages in three. It is concluded from the experimental results that the theory of the local route of infection through the eye cannot account for ectopic schistosomal ocular lesions. Generalized schistosomiasis can be produced by cercarial penetration through either the eyelids or the conjunctiva. It is also concluded that schistosomiasis does not affect the ocular structures, except in the form of rare ectopic lesions. (6 tables, 5 figures, 25 references)—Authors' abstract

LACTIC DEHYDROGENASE ACTIVITY OF AQUEOUS HUMOUR IN RETINOBLASTOMA. Dias, P. L. R., Shanmuganathan, S. S. and Rajaratnam, M. (Dalrymple Hall, 22 Bellhaven Terrace, Glasgow, W.2., Scotland), Brit. J. Ophth. 55:130-132, Feb., 1971.

LDH activity in the aqueous humour of 46 patients with non-malignant intraocular disorders ranged from 0 to 350 units/100 ml. The four cases of retinoblastoma studied gave values of 1800, 2100, 1600, and 3250 units/100 ml. Since LDH activity in the aqueous humour is greatly elevated in retinoblastoma, it seems likely that the estimation of LDH activity in the aqueous humour may be of value in the diagnosis of intraocular malignancy. (2 tables, 7 references)—Authors' abstract

## BULLETIN DE LA SOCIETE BELGE D'OPHTALMOLOGIE

THE OCULAR MANIFESTATIONS OF CONGENITAL ERRORS OF METABOLISM. (French) Goux, J. P. and Kallay, O. (Clinique ophtalmologique de l'Universite de Louvain), Bull. Soc. Belge Ophtal. 157:9-319, 1971.

This excellent monograph begins with an introduction on the relationship of enzyme biochemistry to genetics. The various congenital anomalies are then considered under various headings. The first chapter is on carbohydrate defects such as galactosemia and galactokinase deficiency. The second chapter is on amino acid metabolic problems. The third chapter is on lipids and the fourth chapter is on Wilson's disease. The last two chapters are on specific tissue disorders, diseases of the conjunctiva and bone and epithelial transport disease. (84 figures)—David Shoch

## JAPANESE JOURNAL OF OPHTHALMOLOGY

PORES OF THE TRABECULAR WALL OF SCHLEMM'S CANAL: FERRITIN PERFUSION IN ENUCLEATED HUMAN EYES. Segawa, K. (Ophthalmological Clinic, Shinshu University, Matsumoto-shi, Japan), Jap. J. Ophth. 15:1-8, Jan.-Mar., 1971.

A small quantity of ferritin was injected into the anterior chamber of freshly enucleated human eyes. After a half-hour wait, thin sections were made for electron microscopic study. The ferritin was found to have passed through the trabecular meshwork and the endothelial pores of Schlemm's canal. There was no evidence of an active transport mechanism. (10 figures, 5 references)—Paul A. Hein, Jr.

MACULAR ERG IN CENTRAL SEROUS RETINOPATHY. Nagata, M. and Honda, Y. (Department of Ophthalmology, Tenri Hospital, 200 Mishima-cho, Tenri-city, Nara, Japan), Jap. J. Ophth. 15:9-16, Jan.-Mar., 1971.

Compared with the fellow eye, the eye with central serous retinopathy shows a diminished macular ERG. In thirteen patients with central serous retinopathy treated by photocoagulation, the ERG returned to normal in only two, although all had return of normal visual acuity and loss of the central scotoma. (4 figures, 15 references)—Paul A. Hein, Jr.

EYE INJURY BY ORGANIC PHOSPHORUS INSECTICIDES. Ishikawa, S. (Department of Ophthalmology, University of Tokyo School of Medicine, Tokyo), Jap. J. Ophth. 15:60-68, Jan.-Mar., 1971.

Seventy-one children from an area of Japan heavily treated by helicopter with organic phosphorus insecticides developed eye abnormalities, consisting of narrowed visual fields, reduced visual acuity, optic neuritis, pupillary abnormalities, and altered ocular motility. Treatment with atropine and PAM was efficacious. (5 figures, 11 references)—Paul A. Hein, Jr.

## JOURNAL OF PEDIATRICS

INFANTILE NYSTAGMUS: A PROSPECTIVE STUDY OF SPASMUS NUTANS, CONGENITAL NYSTAGMUS AND UNCLASSIFIED NYSTAGMUS OF INFANCY. Jayalakshmi, P., Scott, T. F., Tucker, S. H. and Schaffer, D. B. (Univ. of Pennsylvania School of Medicine), J. Pediat. 77:177-187, Aug., 1970.

Prospectively collected data on 52 study and 56 control children were used to analyze the diagnostic and prognostic criteria commonly applied to infants with nystagmus. Compared with control children, the affected children had a higher incidence of electroencephalographic abnormalities, strabismus, other neurologic abnormalities, and family history of nystagmus. Except for a higher incidence in multiparous women, no environmental pre- or perinatal circumstances differentiated the study children from control children. Cessation before the fifth year occurred in 70% of those without and in 30% of those with associated strabismus or other neurologic abnormalities. (4 tables, 35 references)—Authors' abstract

RETINAL CHANGES PRODUCED BY PHOTOTHERAPY. Sisson, T. R., Glauser, S. C. Glauser, E. M., Tasman, W. and Kuwabara, T. (Temple Univ. School of Med. and Harvard Univ. School of Med.), J. Pediat. 77:221-227, Aug., 1970.

Phototherapy is used to treat hyperbilirubinemia in the newborn. The potential hazard of retinal damage under such therapy was evaluated using newborn piglets. With electron microscopy, changes in the visual receptors were observed in exposed eyes which were not observed in shielded eyes. Therefore, utmost care would seem to be required to shield the eyes of infants exposed to bilirubin phototherapy units. (6 figures, 7 references)—Joel G. Sacks

SIMULTANEOUS OCCURRENCE OF CONGENITAL ANIRIDIA, HAMARTOMA, AND WILMS' TUMOR. Haicken, B. N. and Miller, D. R. (New York Hospital-Cornell Medical Center, New York), J. Pediat. 78:497-502, Mar., 1971.

The syndrome of Wilms' tumor associated with aniridia consists of congenital nonfamilial aniridia, Wilms' tumor developing before 3 years of age, eye lesions associated with aniridia, mental and growth retardation, microcephaly, genitourinary anomalies and deformities of the pinna. The twenty-fifth case of this syndrome is presented and demonstrates new findings not seen previously: congenital li-

poma and spina bifida with meningocele. This case provides an important link between the Wilms' tumor-aniridia syndrome and disorders of growth control (hemihypertrophy, hamartoma, and visceral cytomegaly syndrome). The array of overlapping congenital malformations occurring with Wilms' tumor, aniridia, and disorders of growth control suggest common teratogenic and oncogenic mechanisms. (1 figure, 1 table, 28 references)—Authors' abstract

## JOURNAL OF NEUROSURGERY

BILATERAL TRAUMATIC ABDUCENS PALSY. Schneider, R. C. and Johnson, F. D. (University of Michigan Medical Center, Ann Arbor), J. Neurosurg. 34:33-37, Jan., 1971.

Two patients with bilateral abducens palsy are presented. A study of the associated injury to the cervical spine suggests that a severe blow to the head in an upward and posterior direction may produce contusion or avulsion of the abducens nerve by the rigid petrosphenoidal ligament under which it passes. (3 figures, 12 references)—Authors' abstract

## KLINISCHE MONATSBLATTER FÜR AUGENHEILKUNDE

EXPERIMENTAL PRODUCTION OF GIANT RETINAL TEARS AND THEIR TREATMENT BY INTRAOCULAR AIR TAMPONADE. (German) Machemer, R., Aaberg, T. and Norton, E. W. D. (Bascom Palmer Eye Institute, University of Miami, Florida), Klin. Mbl. Augenh. 157:1-12, July, 1970.

Giant retinal tears between 90° and 360° could be produced experimentally in the owl monkey eye. After correct positioning of the animal, air was injected into the vitreous cavity to replace all of the vitreous and subretinal fluid and to unfold the retina, and diathermy or cryo was applied to the sclera. Utilizing this technique eight eyes with giant tears between 180° and 350° were successfully reattched. This experimental intraocular air tamponade is hoped to serve as a model for similar human detachments that are not complicated by vitreous strands. (13 figures, 2 tables, 12 references)—Authors' abstract

ANTAGONISTIC EFFECT OF MYDRIATICS AND MIOTICS ON THE OUT-FLOW RESISTANCE OF THE AQUEOUS HUMOUR. (German) Makabe, R. (6 Frankfurt/Main 70, Ludwig-Rehn-Str. 14), Klin. Mbl. Augenh. 157: 30-38, July, 1970.

Tonography was performed in open angle glaucoma suspects after local application of parasympathicolytic, sympathicomimetic and parasympathicomimetic drugs. A significant correlation was observed between the increase in outflow resistance produced by parasympatholytics and a decrease in outflow resistance produced by pilocarpine. However a similar correlation could not be found, when a sympathomimetic and pilocarpine were used. (3 figures, 49 references)—Helmut Buettner

CATARACT AFTER EXTRACORPORAL DIALYSIS. (German) Straub, W. and Freund, J. (355 Marburg/Lahn, Univ. Augenklinik), Klin. Mbl. Augenh. 157:50-52, July, 1970.

A 39-year-old woman with uremia developed bilateral mature cataracts during weekly extra corporal dialysis, which had been going on for several months. The authors suggest that these cataracts are probably caused by osmotic changes during hemodialysis. (2 figures, 4 references)—Helmut Buettner

FLUCTUATIONS OF INTRAOCULAR TENSION DURING HEMODIALYSIS. (German) Reisner, W., Schmidt, P. and Kotzaurek, R. (A-1090 Wien, Alserstr. 4, A-1090 Wien, Lazarettgasse 14, 1. Med. Klinik der Univ. Wien), Klin. Mbl. Augenh. 157: 53-60, July, 1970.

Intravenous injection of hypertonic solutions (i.e. urea) can lower the intraocular pressure (IOP). Lowering the osmotic pressure of the serum, on the other hand, can result in a rise of IOP, due to a delayed reduction of the urea concentration in the aqueous humor and the vitreous. During 25 hemodialysis procedures in seven patients (with normal IOP) the IOP increased significantly. No quantitative correlation between the increase in IOP and the change of osmotic pressure in the serum could be evaluated. However there exists an indirectly proportional correlation between the initial IOP and the degree of increase of the IOP during hemodialysis. (6 figures, 4 tables, 23 references)—Helmut Buettner

DOES THE SCHIØTZ TONOMETER HAVE TO BE DISMANTLED AFTER EACH MEASUREMENT OF INTRAOCULAR PRESSURE? Leydhecker, W. and Sixt, B. (Univ.-Augenklinik Wurzburg), Klin. Mbl. Augenh. 157:65-69, July, 1970.

By means of physical and clinical methods the authors investigated what errors arise, if a Schiøtz tonometer is not dismantled and the tonometer rod not cleaned after each use. Two new methods for the measurement of the friction between the rod and the cylinder have been developed. After five measurements without dismantling the tonometer one error of scale reading already occurs. After 13 measurements, there are two errors in scale readings. Therefore, the tonometer must be dismantled and cleaned after each measurement. (1 figure)—Authors' abstract

THE EFFECT OF PILOCARPINE AND PROSTIGMINE MIXED WITH PILOCARPINE ON THE INTRAOCULAR PRESSURE IN GLAUCOMA SIMPLEX. (German) Stelzer, R. (A-1090 Wien/Österr., Alserstr. 4, II. Univ. Augenklinik), Klin. Mbl. Augenh. 157:74-79, July, 1970.

In 30 eyes with glaucoma simplex pilocarpine (1%) reduced the intraocular pressure (IOP) by 20.7% while the facility of aqueous outflow (C) was increased by 70%. A mixture of pilocarpine (2%) and prostigmine (3%) lowered the IOP by 30.9% and increased the C-value by 150%. (2 figures, 5 tables, 14 references)—Helmut Buettner

FLUORESCEIN ANGIOGRAPHIC FINDINGS IN RETINITIS PUNCTATA ALBESCENS. (German) Makabe, R. (6 Frankfurt, a. M. 70, Ludwig-Rehn-Strasse 14 West-Germany), Klin. Mbl. Augenh. 157:114-118, July, 1970.

An 18-year-old white woman complaining about progressive loss of night vision presented the typical fundus changes of retinitis punctata albescens. She had a decreased visual acuity, concentrically constricted visual fields with a ring scotoma, a diminished and retarded dark adaptation, impaired color perception and no ERG response. Fluorescein angiography showed early fluorescence of the white spots in the fundus, suggesting that these are areas with a defect of the pigment epithelium. (5 figures, 14 references)—Helmut Buettner

RUBELLAR EMBRYOPATHY OF THE EYE. (German (Töndury, G. (CH-8006 Zürich, Schweiz, Anatom. Univ.-Institut), Klin. Mbl. Augenh. 157:141-164, Aug., 1970.

Fifty-four of 102 embryos and fetuses whose mothers had rubella during the first trimester of pregnancy, showed heart lesions (46) and cataracts (38). The combination of cataract and cardiac lesions was present in 30 cases. The chronic process of destruction of the lens, even persisting in the postnatal period due to continuous presence of the rubella virus in the affected structures, begins 10 to 12 days after manifestation of the disease in the mother. The primary lens fibers swell and later disintegrate. The same happens to the newly formed secondary lens fibers at the equator, which are continuously added in the periphery. This results in a lens with a liquified embryonal nucleus and a thin cortical layer of secondary lens fibers.

More rare findings were: atrophic and abnormally short iris with poorly developed sphincter muscle and atrophic ciliary body (in 4 cases) and microphthalmos combined with lenticular and corneal malformation (in 4 cases). There were no inflammatory signs (i.e. iridocyclitis) in all these cases. Up to the seventh month, embryos and fetuses cannot respond with cellular reaction. The only response to a virus infection is a necrosis of the affected cells. (18 figures, 1 table, 44 references)—Helmut Buettner

DIAGNOSIS OF OCULAR MYASTHENIA IN CHILDREN. (German) Manz, F. and Schmidt, D. (78 Freiburg, Hansastr. 9, Neurol. Klinik mit Abt. f. Neurophys.; 78, Freiburg, Killianstr., Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157: 173-182, Aug., 1970.

Ocular symptoms of myasthenia gravis are very common and often the earliest manifestation of this disease. About 10% of all cases of myasthenia have their onset before the age of 15. Therefore this disease should be considered in all children with paresis of the extraocular muscles. The tensilon- and prostigmine- test, which can be performed as an office procedure, provides a decisive diagnosis in most cases. In doubtful cases or when more subtle examinations are desired, stimulation electromyogra-

phy, needle electromyography or registration of the opto-kinetic nystagmus before and after administration of cholinesterase inhibitors may be performed. (9 figures, 3 tables, 39 references)—Helmut Buettner

THE EFFECT OF CATAPRESAN (R) ON THE INTRAOCULAR PRESSURE (IOP). (German) Heilmann, K. (8 München 80, Ismaningerstr. 22, Augenklinik der Techn. Hochschule, West-Germany), Klin. Mbl. Augenh. 157:182-192, Aug., 1970.

2-(2,6-dichlorphenyl amino) 2-imidazoline-hydrochloride (Catapresan (R)), an antihypertensive drug, lowers the IOP significantly, when applied locally. It is free from local side-effects and does not produce miosis. However, general side effects such as a considerable decrease in blood pressure, a dryness of mucous membranes and a sedative effect still prevent the routine use of this drug in the treatment of glaucoma. A comparative study of the effects of a 0.5% and a 0.25% solution of Catapresan (R) in 17 patients with primary glaucoma showed more general side effects when using 0.5% Catapresan (R) locally, while the IOP was lowered to the same extent by both concentrations. (4 figures, 3 tables, 4 references) —Helmut Buettner

SERUM GLYCOPROTEID LEVEL AND DIABETIC RETINOPATHY. (German) Langness, U., Thiel, H. J. and Moog, E. (23 Kiel, Hegewischstr. 2, Univ. Augenklinik; 23 Kiel, Metzstr. 53/57, II. Med. Klinik u. Poliklinik der Univ. West-Germany), Klin. Mbl. Augenh. 157:202-208, Aug., 1970.

The serum level of protein-bound amino sugars (glycoproteids) is known to be elevated in diabetics and especially so in diabetic angiopathy. Of 121 diabetics (19 to 60 years of age) 11 had diabetic microangiopathy of the retinal vasculature; four years later eight more had developed diabetic retinopathy, regardless of whether the diabetes had been well treated or not. All 121 patients had a significantly elevated serum glycoproteid level, even before changes of their retinal vessels were detected. The authors think that it might be possible to predict the onset of diabetic retinopathy by determining individual glycoproteid fractions in the serum. (3 tables, 36 references)—Helmut Buettner

MALIGNANT CHOROIDAL MELANOMA AND THE CILIARY NERVE. (German) Vogel, M. H. (43 Essen, Hufelandstr. 55, Univ. Augenklinik, Klinikum Essen, West-Germany), Klin. Mbl. Augenh. 157:215-224, Aug., 1970.

In 17 out of 20 malignant melanomas of the choroid, a ciliary nerve was found in the area of the tumor base on histological examination. This nerve was covered by a more or less thick layer of nevus cells which showed a gradual transition into the tumor tissue. Choroidal nevi have been designated as the site of origin of the malignant melanomas of the choroid. The idea is advocated that the nevus cells are proliferated Schwann's sheath-cells of the ciliary nerves. This interpretation is in accordance with the opinions of the neurogenic origin of malignant choroidal melanoma which have been propagated in the literature. It also would explain the frequency of malignant choroidal melanomas at the posterior pole of the eye. (8 figures, 16 references)—Author's abstract

FUNDUS AND HISTOLOGICAL FINDINGS IN INFANTS WITH PACHYMENINGEOSIS HAEMORRHAGICA INTERNA. (German) Schmidt, B. and Trojan, H. J. (355 Marburg/Lahn, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:239-244, Aug., 1970.

Multiple subhyaloid hemorrhages, sometimes associated with papilledema, point to the diagnosis of pachymeningiosis hemorrhagica interna. Three well documented cases of this disease in infants are reported. (6 figures, 4 references)—Helmut Buettner

LYMPHATIC TUMORS OF THE EYE AND ADNEXA. (German) Stärk, N. and Thiel, H. J. (6000 Frankfurt/Main, Ludwig-Rehn-Str. 14, Univ. Augenkl.; 23 Kiel, Hegewischstr., Univ. Augenkl. West-Germany), Klin. Mbl. Augenh. 157:308-326, Sept., 1970.

Primary lymphatic tumors may be divided into three groups: 1) reactive hyperplasias 2) sarcomas of the lymphoreticular tissues and 3) progressive autonomous hyperplasias, which have all the sarcoma characteristics except for the extensive and destructive growth of sarcomas. The histological diagnosis of these tu-

mors is often very difficult or even impossible, especially as to determination of malignancy or non-malignancy. However, the treatment of choice seems to be early irradiation, as shown by an evaluation of 36 cases of ocular lymphomas. (12 figures, 5 tables, 34 references)—Helmut Buettner

TONOGRAPHIC INVESTIGATIONS DURING TREATMENT WITH LOCAL INJECTION OF DEXAMETHASONE. (German) Neumann, M. and Hiller, H. (X 69 Jena/DDR, Bachstr. 18, Univ. Augenklinik East-Germany), Klin. Mbl. Augenh. 157:334-342, Sept., 1970.

Tonography—performed in 15 patients, who received subconjunctival (2.5 mg) or retrobulbar (5 mg) dexamethasone injections for treatment of uveitis—revealed a significant increase in intraocular pressure (IOP) and aqueous humor secretion, while the resistance to aqueous out-flow was unaffected. The elevated IOP was transitory and never reached pathological values (more than 26 mm Hg). (4 tables, 22 references)—Helmut Buettner

THE DEBRÉ-LAMY-LYELL SYNDROME. (German) Reich, H. and Jünemann, G. (44 Münster i. W., v. Esmarchstr. 56, Univ. Hautklinik; 44 Münster i. W., Westring 15, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:358-365, Sept., 1970.

Lyell's syndrome (toxic epidermal necrolysis) was first described by the French pediatricians Debré, Lamy and Lamotte in 1939, prior to Lyell's publication in 1956. It is characterized by extensive necrolytic dermal lesions combined with ocular involvement such as conjunctival scarring, symblepheron formation and corneal infiltration or ulceration, often followed by perforation. This disease has a mortality of 30%. In addition to a certain predisposition, drugs (sulfonamides, pyrazolone derivatives, antibiotics and barbiturates), viruses and bacteria (Staphylococcus pyogenes) can cause this dangerous disease. Five case reports are included in this paper. (5 figures, 19 references)—Helmut Buettner

REGENERATION OF DARK ADAPTATION IN SURGICALLY REATTACHED RETINAS. (German) Hammerstein, W. (4 Düsseldorf, Moorenstr. 5, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:385-388, Sept., 1970.

Twenty-four out of 25 eyes with retinal detachments showed progressive normalization of the dark adaptation curve postoperatively. One eye, which did not recover, had a detachment of several years duration. This suggests, that recovery of retinal function depends on the duration of the retinal detachment. (1 figure, 1 table, 27 references)—Helmut Buettner

ERG AND EOG POTENTIALS AFTER LONG TERM RESOCHIN ADMINISTRATION. (German) Svěrák, J., Erbenová, Z., Peregrin, J. and Salavec, M. (582 Hradec Králové Königgrätz/CSSR, Univ. Augenklinik), Klin. Mbl. Augenh. 157:389-392, Sept., 1970.

Of 32 patients, receiving Resochin for at least six years (average total dose 572 g.) for treatment of chronic polyarthritis, 87% had a significant decrease of the b-wave amplitude of the ERG and 47% had a pathologically low EOG activity. All patients had normal appearing fundi. (2 figures, 33 references)—Helmut Buettner

CHANGES OF THE STANDING POTENTIALS OF THE EYE (EOG) IN CHOROIDAL DETACHMENT. (German) Alexandridis, E. (69 Heidelberg, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:395-399, Sept., 1970.

In three eyes with choroidal detachments the EOG-amplitudes were markedly reduced or even extinguished, depending on the size of the detachments. Following surgical reattachment of the choroid the EOG recovered rapidly and 10 to 11 days later it was absolutely normal. (3 figures, 15 references)—Helmut Buettner

PERIPHERAL IRIDECTOMY WITH CAUTERIZATION OF THE SCLERAL (SCHEIE'S PROCEDURE). 3. COMPLICATIONS. (German) Polychronakos, D. J. and Chryssafis, B. (Thessaloniki/Griechenland, Aristoteles Str. 10), Klin. Mbl. Augenh. 157:463-475, Oct., 1970.

Five hundred Scheie's procedures are analyzed with regard to their complications. The

incidence of synechia, cataract, vitreous prolapse and loss, flat anterior chamber and malignant glaucoma is almost the same as in any other fistulating operation. Sympathetic ophthalmia has so far never been observed after a Scheie's procedure. The incidence of late infections, however, has been unexpectedly high, 2.2% in this study. (4 tables, 20 references)—Helmut Buettner

A NEW METHOD FOR THE FILM FIXATION OF THE KERATOPROSTHESIS IN THE HOST TISSUE. (German) Faulborn, J. (78 Freiburg/Br. Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:476-487, Oct., 1970.

After implantation of a keratoprosthesis into subcutaneous tissue, a capsule of connective tissue is formed around the prosthesis. On transplantation into the eye, the connective tissue behaves like an autotransplant, into which the prosthesis is firmly embedded. The first clinical and histological observations in four rabbit eyes have shown that two and four months after the transplantation of the autoallotransplant into the eye, a firm connection exists with the host tissue. (12 figures, 6 references)—Author's abstract

TENSILE STRENGTH OF RABBIT CORNEA AFTER PERFORATING INJURY AND ETHYL-DEOXYURIDINE (EDU) ADMINISTRATION. (German) de Decker, W. (23 Kiel, Univ. Augenklinik, West-Germany), Klin. Mbl. Augenh. 157:487-492, Oct., 1970.

In 1967 another virostatic agent, EDU, was introduced into therapy of corneal herpes. It is as effective as iodine-deoxy-uridine (IDU), but better tolerated by the corneal tissue. Comparative measurements of tensile strength of corneal scars after perforating injuries treated with and without EDU showed, that the administration of EDU improved wound healing. (2 figures, 1 table, 12 references)—Helmut Buettner

PHOTOCOAGULATION IN INFLAMMATORY DISEASES OF THE FUNDUS. Heydenreich, A. (Univ.-Augenklinik Jena), Klin. Mbl. Augenh. 157:610-617, Nov., 1970.

Photocoagulation is a valuable support for conservative drug therapy in inflammatory diseases of the fundus. In choroiditis, in particular, isolated patches or relapses at the marginal zones of older patches were coagulated. With this procedure, the clinical course of the disease could be shortened and the progressive character of the disease could be brought under control. In retinal periphlebitis, spot coagulation of bleeding vascular areas combined with fluorescein ophthalmoscopy brought about scarring of these areas and thus prevented recurrent hemorrhages in 42% of the cases. In a similar way, focal areas were coagulated in retinitis centralis serosa. In Coats' disease, secondary retinoschisis, secondary retinal detachment and secondary retinal foramen, the pathological areas were sealed by coagulation and spreading of these processes to healthy retinal areas was prevented. (10 figures, 1 table, 15 references)—Author's abstract

ULTRASOUND-ECHOGRAPHY—AN IMPORTANT AUXILIARY EXAMINATION IN RETINAL DETACHMENT SURGERY. (German) Freyler, H. (A-1090 Wien, Spitalgasse 2, I. Univ. Augenklinik, Schweitz), Klin. Mbl. Augenh. 157:617-633, Nov., 1970.

Echography can provide pertinent pre-, intra- and post-operative information in retinal detachments. Especially in eyes with opaque media, this method has proven to be very valuable in retinal detachment surgery. (8 figures, 29 references)—Author's abstract

DEVELOPMENT OF CHOROIDAL VESSELS IN THE MACULAR AREA. (German) Heimann, K. (5 Köln-Lindenthal 41, Univ. Augenklinik West-Germany), Klin. Mbl. Augenh. 157:636-642, Nov., 1970.

The authors studied in embryos and fetuses the development of the choroidal vessels by means of indian ink- and neoprene-injection. In the macular area the short ciliary arteries form a dense and well anastomosing network of choroidal arterioles, emphasizing the particular hemodynamic conditions of this area. This pattern of choroidal vessels differs markedly from the rest of the choroid and can explain the predilection of the posterior pole for inflammatory and degenerative lesions, for example congenital toxoplasmosis. (5 figures, 15 references)—Helmut Buettner

FAMILIAL INCIDENCE OF THE BLOCH-SULZBERGER-SYNDROME (INCONTINENTIA PIG-

MENTI) WITH OCULAR INVOLVEMENT. (German) Benedikt, O. and Ehalt, H. (A-8036, Graz, Auenbruggerplatz 4 Univ. Augenklinik,), Klin. Mbl. Augenh. 157: 652-663, Nov., 1970.

Papulo-macular and vesicular changes with streak-like deposits of melanin pigment in the skin (incontinentia pigmenti) can be associated with ocular anomalies, such as corneal opacifications, congenital cataracts, iris malformations, persistent hyperplastic primary vitreous, pseudoglioma, uveitis, chorioretinitis with subsequent optic atrophy, retinal folds, hydrophthalmus, nystagmus and strabismus. This disease starts in early infancy and is predominently found in females. The authors report two cases of Bloch-Sulzberger syndrome in one family (mother and daughter) with ocular involvement. The daughter's left eye was removed under the assumption of an existing retinoblastoma. Histological examination revealed persistent hyperplastic primary vitreous with a persistent hyaloid artery and retinal dysplasia. The authors assume, that this syndrome represents a sex-linked hereditary disease. (9 figures, 33 references)—Helmut Buettner

IRRADIATION THERAPY OF LYMPHOMAS IN THE OCULAR REGION. (German) Stärk, N. and Pánek, V. (6000 Frankfurt/Main, Ludwig-Rehn-Str. 14, Univ. Augenklinik; 6000 Frankfurt/Main, Univ. Klinik f. Strahlentherapie, West-Germany), Klin. Mbl. Augenh. 157:693-697, Nov., 1970.

In seven cases of localized lymphomas (three histological proven malignant) beta-irradiation proved to be very effective. Therefore irradiation should always be preferred to mutilating radical surgery. (1 table, 13 references)—Helmut Buettner

ELECTRON MICROSCOPIC FINDINGS IN KERATOCONUS. (German) Göttinger, W. and Auböck, L. (A-8036 Graz, Univ. Augenklinik; A-8036 Graz, Path. Univ. Inst.), Klin. Mbl. Augenh. 157:762-772, Dec., 1970.

Phagocytizing stromal cells and large amounts of collagen fibril precursor material were found in six corneas of patients with keratoconus. These changes may be the expression of an enzymatic defect in fibrillogenesis, resulting in the malformation of the cornea. The theory of an enzymatic defect fits well with the interpretation of keratoconus being a hereditary disease. (9 figures, 19 references)—Helmut Buettner

## LANCET

HEADACHE AND THE EYE. A COMMUNITY STUDY. Waters, W. E. (Dept. of Social Medicine, Oxford University, England), Lancet 7662:1-4, 1970.

Groups of individuals with headache, unilateral headache, or migraine, and a group who had not had a headache in the previous year, were identified by questionnaire in a random sample of a general population. Four hundred and fourteen individuals were examined for visual acuity and ocular-muscle imbalance. These tests gave little evidence that visual defects were more frequent in those with headache or those with migraine compared with individuals without headache in the same population. The only statistically significant difference found between the four groups was that hyperphoria with near vision was more frequent in the migraine group. It is concluded that, in the general population, headaches are seldom caused by defects in visual acuity or ocular-muscle imbalance. (3 figures, 4 tables, 11 references)—Author's abstract

## NEW ENGLAND JOURNAL OF MEDICINE

NORRIE'S DISEASE—AN X-LINKED SYNDROME OF RETINAL MALFORMATION, MENTAL RETARDATION AND DEAFNESS. Holmes, L. B. (Massachusetts General Hospital, Boston), N. Eng. J. Med. 284:367-368, 1971.

A family in which six males in four generations were affected with Norrie's disease (an X-linked syndrome of retinal malformation, mental retardation and deafness), the initial diagnoses of retrolental fibroplasia, pseudoglioma, and congenital toxoplasmosis had been suggested. The general lack of awareness of this syndrome is probably responsible for these incorrect diagnoses. Because of the devastating nature of the syndrome and the lack of any effective treatment, some parents may seek prenatal sex identification in all subsequent pregnancies and plan to abort all unborn

males. (2 figures, 5 references)—Joel G. Sacks

## TRANSACTIONS OF THE AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARNGOLOGY

COLOR ENHANCEMENT OF BRAIN AND ORBITAL SCANS IN PROPTOSIS. Kramer, S. G., Archer, D. D., Polcyn, R. E., Charleston, D. B. and Yasillo, N. (University of Chicago, 950 E. 59th St., Chicago, Illinois), Tr. Am. Acad. Ophth. Otolaryng. 74: 1240-1248, Nov.-Dec., 1970.

Thirty-three patients with orbital disease were evaluated by radioisotope scanning of the brain and orbits with sodium pertechnetate-99m (NaTc04)—a technique virtually unattended by hazard or morbidity. Ordinary interpretation of such scans is frequently difficult because of high background activity in the orbital regions which obscures orbital detail. This study utilized an electronic color enhancement technique to increase the ease and accuracy of scan interpretations. No scan of a patient with an intra-orbital mass was interpreted as negative, and no scan of a patient without a mass was interpreted as positive by this technique. Masses were correctly localized with respect to the globe in 13 of 14 positive scans. Radioisotope scanning of the orbits particularly when aided by color enhancement, proves to be a simple and accurate diagnostic aid for detecting and localizing intra-orbital masses. (3 tables, 2 figures, 18 references)—Authors' abstract

SUB-TENON STEROID INJECTION FOR OPTIC NEURITIS. Smith, J. L., McCrary, J. A., Bird, A. C., Kurstin, J., Kulvin, S. M., Skilling, Jr., F. D., Acers, T. E. and Coston, T. O. (University of Miami School of Medicine, Florida), Tr. Am. Acad. Ophth. Otolaryng. 74:1249-1253, Nov.-Dec., 1970.

Steroids injected in the sub-Tenon's space have been helpful in the management of optic neuritis. This route of administration is easier, safe, and less painful than retrobulbar injection. We prefer to use aqueous triamcinolone. The clinical response to this drug lasts one to two weeks after a single injection. The effects of the drug, administered as we have described, warrant further clinical study in the treatment of ischemic optic neuritis and congestive thyroid exophthalmos. (1 table, 4 references)—Authors' abstract

LYELL'S DISEASE, THE STEVENS-JOHNSON SYNDROME, AND EXFOLIATIVE DERMATITIS. Ostler, H. B., Conant, M. A. and Groundwater, J. (University of California San Francisco Medical Center), Tr. Am. Acad. Ophth. Otolaryng. 74:1254-1265, Nov.-Dec., 1970.

A case of Lyell's disease has been presented. On the basis of observation and a partial review of the literature, the disease has been compared clinically, histologically, and etiologically with the Stevens-Johnson syndrome and exfoliative dermatitis. Typical Lyell's disease appears to be a clinical and pathologic entity, distinct from other dermatologic disorders. Since there are only a limited number of ways in which skin and mucous membranes can react to disease, it is not surprising that Lyell's disease often resembles other mucocutaneous diseases in one or more respects. (6 figures, 5 tables, 16 references)—Authors' abstract

AUTOMATIC OBJECTIVE REFRACTION: REPORT OF A CLINICAL TRIAL. Safir, A., Knoll, H. and Mohrman, R. (Mount Sinai School of Medicine, New York), Tr. Am. Acad. Ophth. Otolaryng. 74:1266-1275, Nov.-Dec., 1970.

Objective techniques of refraction which are currently used are objective only in the sense that they do not require the subjective response of the patient, but they do require the subjective response of the examiner. A truly objective instrument for determining refractive error has been designed and built. This instrument may be operated satisfactorily by a person untrained in refraction. The result of the measurement of the refractive state of the subject is provided in the form of a written record. An analysis is presented of a clinical test evaluating the performance of the instrument as compared to the results obtained by a panel of practitioners examining the same patient sample. It is concluded that the new instrument provides a measure of refractive error that is equivalent to that obtained by streak retinoscopy. (8 figures, 4 references)—Authors' abstract

MARGINAL (RING) CORNEAL ULCER AS PRESENTING MANIFESTATION OF WEGENER'S GRANULOMA: A CLINICOPATHOLOGIC STUDY. Ferry, A. P. and Leopold, I. H. (Mount Sinai School of Medicine, City University of New York), Tr. Am. Acad. Ophth. Otolaryng. 74:1276-1282, Nov.-Dec., 1970.

Marginal (ring) ulcers of the cornea are frequently symptomatic rather than primary. A case is reported in which a ring ulcer of the cornea was one of the earliest manifestations of Wegener's granuloma. On pathologic examination of the eye, a granulomatous reaction to corneal collagen fibers was found in the walls of the ring ulcer. This observation supports the concept that abnormal immune mechanisms play a major role in the pathogenesis of Wegener's granuloma. Appropriate management by the ophthalmologist of a patient with a ring ulcer includes both care of the corneal lesion and a search for a possible underlying systemic disease. (8 figures, 8 references)—Authors' abstract

A SCLERAL PATCH FOR EXPOSED IMPLANTS. Helveston, E. M. (Indianapolis, Indiana), Tr. Am. Acad. Ophth. Otolaryng. 74: 1307-1310, Nov.-Dec., 1970.

A new procedure has been described which employs human eye bank sclera as a patching material for use in retention or replacement of an extruding or extruded orbital implant. (5 figures, 4 references)—Author's abstract

SIMULTANEOUS BILATERAL UVEAL MELANOMAS RESPONDING TO BCNU THERAPY. Stark, Jr., W. J., Rosenthal, A. R., Mullins, G. M. and Green, W. R. (Wilmer Institute, the Johns Hopkins University and Hospital, Baltimore), Tr. Am. Acad. Ophth. Otolaryng. 75:70-83, Jan.-Feb., 1971.

To our knowledge, this patient is the first to be treated for intraocular melanoma with BCNU. The dramatic therapeutic response to BCNU represents a significant departure from the results usually obtained in the treatment of metastatic ocular melanoma, as seen from a review of the literature. Consequently, we believe further trials with BCNU are indicated in cases of intraocular melanoma that are not amenable to surgery. (12 figures, 31 references)—Authors' abstract

CONSERVATIVE TREATMENT OF INTRAOCULAR MELANOMAS. Long, R. S., Galin, M. A. and Rotman, M. (New York Medical College, New York), Tr. Am. Acad. Ophth. Otolaryng. 75:84-93, Jan.-Feb. 1971.

Choroidal malignant melanomas have been treated with cobalt 60 plaques. A computerized technique is used to assess the duration of treatment and the method for fractionation of the dose. These tumors are responsive to this form of therapy, and ocular function may be preserved while the neoplasm is eliminated. (3 tables, 5 figures, 17 references)—Authors' abstract

EFFECT OF RADIATION THERAPY ON METASTATIC CHOROIDAL TUMORS. Jaeger, E. A., Frayer, W. C., Southard, M. E. and Kramer, S. (Jefferson Medical College of Thomas Jefferson University, Philadelphia), Tr. Am. Acad. Ophth. Otolaryng. 75:94-101, Jan.-Feb., 1971.

This report describes our experiences in the use of irradiation to treat metastatic tumors of the choroid in 21 eyes of 15 patients, and points out several factors of interest. Consideration perhaps should be given to the use of larger doses of initial radiation than was used in this series of patients, and to repeat treatment if a residual tumor is present. It was not possible to correlate the degree of malignancy of the primary tumor and response of the choroidal metastasis to ocular irradiation. While irradiation of these ocular tumors must be considered a palliative measure, this technique does offer preservation of useful vision in some instances. No ill effects were observed from radiation treatment. (2 tables, 4 figures, 10 references)—Authors' abstract

MALIGNANT CELLS IN THE BLOOD OF EYE PATIENTS. Stanford, G. B. and Reese, A. B. (University of Utah Medical School, Salt Lake City), Tr. Am. Acad. Ophth. Otolaryng. 75:102-109, Jan.-Feb., 1971.

At the present time, discovery of malignant cells in the blood of a patient has little prognostic significance. The one exception occurs

when a shower of cells is isolated during surgery. Results from some human clinical studies indicate that the five-year survival rate is cut in half under these circumstances. Theoretically, the natural resistance is impaired by operative stress, and a shower of cells is not as easily destroyed at this time. There is no justification at present for altering or withholding curative therapy on the basis of malignant cells which are demonstrated in a preoperative blood sample taken from a patient with an otherwise potentially curable lesion. After the postoperative period, persistent appearances of malignant cells in the blood of a patient who has undergone a curative-type resection may indicate the need for additional roentgen-ray therapy or chemotherapy. Because an established trend indicates a 50% survival rate in patients who are found to have a shower of malignant cells at the time of surgery, every effort should be made to prevent dissemination at the time of treatment of eye tumors. (6 figures, 16 references)—Authors' abstract

PIGMENTED NEVI OF THE CHOROID. CLINICAL STUDY OF SECONDARY CHANGES IN THE OVERLYING TISSUES. Naumann, G. O., Hellner, K. and Naumann, L. R. (Universitats-Augenklinik, Hamburg, Germany), Tr. Am. Acad. Ophth. Otolaryng. 75:110-123, Jan.-Feb., 1971.

This report describes clinical observations on 124 choroidal nevi in 112 patients who were reexamined periodically for an average of two years . . . The concept that the vast majority of malignant melanomas develop from preexisting nevi is supported by our observations on the location and sex distribution of the lesion, which are quite similar in both, and by the high frequency of choroidal nevi in eyes enucleated at autopsy. The secondary changes in the overlying tissues caused by many choroidal nevi complicate the separation of small malignant melanomas from nevi. Careful long-term follow-up examination, including fluorescein angiography, infrared fundus photography, and perimetry are necessary to rule out malignant transformation. (10 figures, 48 references)—Authors' abstract

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OPHTHALMIC MINIATURE

We know from their preserved spectacles that the hypermetropes included Hindenburg (+4.5 D) and Martin Luther (+3.0 D), while Bismarck (−3.0 D), Schopenhauer (−3.5 D), Goethe (−6.0 D), Schiller (−2.75 D), and George Washington were all myopes.

Patrick D. Trevor-Roper
*The World Through Blunted Sight*
New York, Bobbs-Merrill, p. 16

# NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
*700 North Michigan Avenue, Chicago, Illinois 60611*

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### FIFTH AFRO-ASIAN CONGRESS OF OPHTHALMOLOGY

The fifth Afro-Asian Congress of Ophthalmology will be held at Nissei Kaikan Hall, Tokyo, Japan, July 9-12, 1972. The main subjects are infection of the eye and management of glaucoma, with symposia on the cornea, cataract surgery, and contact lenses. For further information contact Prof. Akira Nakajima, Secretary General, The Japanese Organizing Committee for the fifth Afro-Asian Congress of Ophthalmology, Department of Ophthalmology, Juntendo University, Hongo, Bunkyo-ku, Tokyo, Japan 113. Prof. Yukihiko Mitsui is president of the local organizing committee and Dr. Yukio Kogure is treasurer.

### FIRST INTERNATIONAL SURGICAL EYE SYMPOSIUM

The First International Surgical Eye Symposium will be held in Bologna, Italy, on April 23-27, 1972. Refined surgical techniques in the management of the chamber angle in glaucoma, congenital and senile cataracts, corneal lesions, prosthetokeratoplasties and plastic surgery of the eyelids and orbit will be demonstrated. Operative sessions will be televised. Papers on these subjects and concerning recent advances in orbitography, ultrasonography, and fluorescein angiography will be presented.

For information contact the Clinica Oculistica, Universita di Bologna via Massarenti, 9—Bologna, Italy.

### PACIFIC MEDICAL CENTER: STRABISMUS CONFERENCE

The Pacific Medical Center, San Francisco, will hold a conference on strabismus October 28-30, 1971. This conference will cover new physiologic information, clinically applicable tests, and surgical approaches. Clinical problems will be emphasized and discussed in a round table format.

The fee is $125. For information: Arthur Jampolsky, M.D., Chairman, Department of Continuing Education, Pacific Medical Center, Clary and Webster, San Francisco, California 94115.

### RESEARCH STUDY CLUB: OPHTHALMOLOGY MEETING

The Research Study Club of Los Angeles will hold their 41st annual mid-winter convention in ophthalmology and otolaryngology, January 23-28, 1972, at the Los Angeles Hilton Hotel, Los Angeles.

The guest speakers on ophthalmology will be Giambattista Bietti, Rome, Italy; Alejandro Salleras, Buenos Aires, Argentina; Marshall M. Parks, Washington, D.C.; Michael J. Hogan, San Francisco, California; Dohrmann K. Pischel, San Francisco, California; and Lester T. Jones, Portland, Oregon. A cadaver course will be conducted at the University of Southern California School of Medicine.

### FDA APPOINTS OPHTHALMOLOGICAL ADVISORY GROUP

The Food and Drug Administration announces the appointment of an Ophthalmological Advisory Group. A. Edward Maumenee, Wilmer Institute, is chairman of the committee. Other committee members are James Allen, Tulane University; Bernard Becker, Washington University; Jerome Goldman, Washington Hospital Center; Peter Laibson, Wills Eye Hospital; Irving H. Leopold, Mt. Sinai Hospital, John McTigue, George Washington Hospital, and Maurice Rabb, Illinois University School of Medicine.

### CALL FOR PAPERS: RADIATION EFFECTS

The National Academy of Sciences invites submission of current data on somatic, genetic, and environmental effects of low-level ionizing radiation, including effects on human growth and development. This material is requested whether or not it has been published, but work in progress, not yet reported, is of particular interest. The request is made in order to assist an advisory committee of the National Research Council in its deliberations concerning ionizing radiation effects on human populations. Please send material to Dr. A. W. Hilberg, Division of Medical Sciences, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C. 20418.

### LEARNING DISABILITIES CONFERENCE: ORTON SOCIETY

The 22nd annual national conference on language-learning disabilities (dyslexia) of the Orton Society will be held November 4-7, 1971, at the Statler-Hilton Hotel, Boston, Massachusetts. The theme is language disability in the clinic and the classroom. For further information contact the Orton Society, Inc., 8415 Bellona Lane, Towson, Maryland 21204.

### NATIONAL EYE INSTITUTE APPROPRIATION FOR 1972

On August 10, 1971, President Nixon signed into

law the appropriations bill agreed upon by the House of Representatives and Senate, granting the National Eye Institute $37,255,500 for the fiscal year of 1972 (July 1, 1971, through June 30, 1972). This is an increase of $7 million over last year. The scientific fellowship program in ophthalmology was decreased $800,000 from $1.7 million, thus reducing the number of fellows that can be supported from 123 to 52.

### Annual conference: Wills Eye Hospital

The 24th annual conference of the Wills Eye Hospital will be held February 3-5, 1972, at the Bellevue Stratford Hotel in Philadelphia. The Bedell lecture will be given by Lorenz E. Zimmerman, and there will be symposia on cataracts with work shops on retina and refraction. For further information contact Robert D. Mulberger, M.D., Chairman, Conference Committee, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pennsylvania 19130.

### Society of Military Ophthalmologists

The Society of Military Ophthalmologists annual meeting will be held September 20, 1971, at 6:00 P.M. at the Stardust Hotel, Las Vegas. After the traditional collation, Byron Smith will lecture on oculoplastic rehabilitation. A short business meeting follows. All members are urged to attend.

## Personals

### Robert Machemer

Robert Machemer has been named the first Louis B. Mayer Scholar by Research to Prevent Blindness, Inc. He is thus the recipient of a $25,000 grant under RPB's new Scholars Program. The grant is made possible by an initial three-year $75,000 gift to RPB from the Louis B. Mayer Foundation, Beverly Hills, California. Additional grants of $25,000 will be made to different scientist each year under terms of the Scholars Program.

Dr. Machemer was born in Munster, Germany, in 1933, and received his medical education in that country. He came to the United States in 1966 as a Research Fellow at the Bascom Palmer Eye Institute, University of Miami School of Medicine, and was appointed assistant professor in that school's department of ophthalmology in June, 1970. He has been chief of the ophthalmology section of Miami's Veterans Hospital since 1968.

### Hermann M. Burian

Hermann M. Burian has retired from the University of Iowa as Emeritus Professor of Ophthalmology. He was made Clinical Professor of Ophthalmology at the University of North Carolina School of Medicine, and since July 1, his new home is at 1303 Wildwood Drive, Chapel Hill.

Louisiana State University School of Medicine

Department of Ophthalmology

and

The Eye Foundation of America

# SYMPOSIUM ON GLAUCOMA

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David Apple, M.D.
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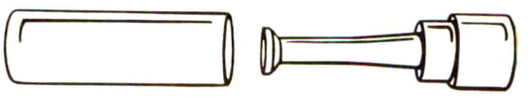
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## TOPICS

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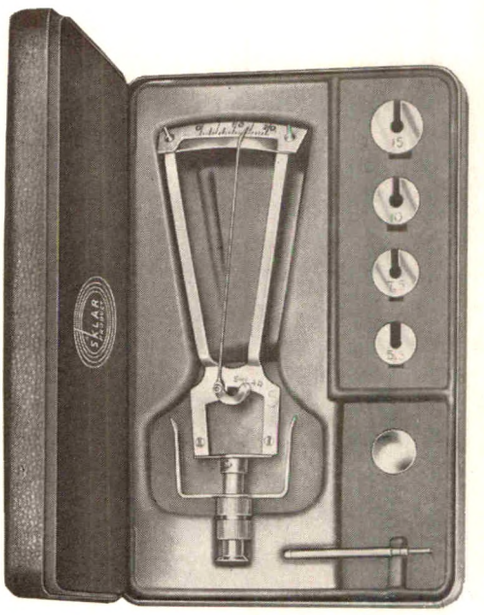
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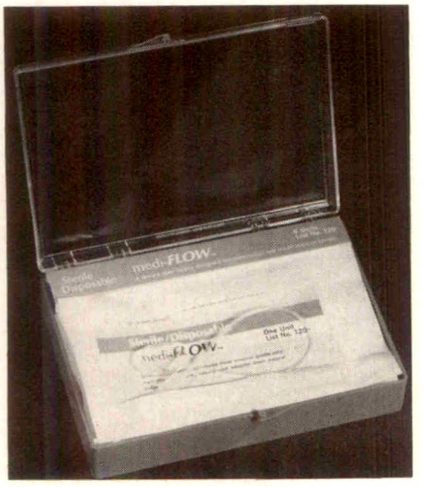
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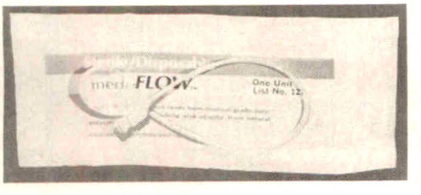
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*JAMA *214*:5 (Nov. 2, 1970), 835-6

# UNREALISTIC DEMANDS ON SCIENCE AND MEDICINE

To serve the public most effectively, scientists, engineers, and physicians need a friendly, sympathetic environment and one in which their limitations are understood. Until recently such an environment prevailed, but the last few years have brought changes in the public's attitudes. Many adverse changes are involved, but one of the most important is the public's inaccurate estimate of what can be achieved. The public has come to expect miracles from engineering and medicine.

Today medical scientists and physicians are particularly subject to pressures produced by unrealistic demands from the public. Failure to produce miracles is taken as proof of a refusal to be interested in meeting the public's desires. One indignant correspondent wrote me in part as follows:

"It would certainly seem, from the record to date, that basic research scientists are so preoccupied with the exquisiteness of their protocols and the refinements of their research approaches that they have missed entirely the objective and intent of we taxpayers who are funding their 'ivory tower isolationism' . . . we as taxpayers expect something more in return than scientific dialogue between the scientists at seminars and in medical journals."

During a recent discussion concerning the new cancer program, similar remarks were made. If the critics are unwilling to grant humane motives to medical scientists, they should at least recognize the power of self-interest. Anyone responsible for a dramatic advance in the fight against cancer will receive recognition and undying fame.

In some aspects of medicine, physicians can perform today what would have been impossible 40 years ago. Yet there are other aspects in which the practice of medicine has not changed much. For example, little can be done to halt the aging process. Neurologic disorders are another area in which the medical profession cannot deliver as much as people wish.

Physicians find that many patients have unrealistic ideas of what doctors can do for them. Many people seem to think that they can carelessly expend physical resources in any way they wish and that the doctor can always cure them. Patients give no cooperation in the matter of exercise, diet, or abstinence from heavy smoking and yet expect the doctor to make up for their neglect. They want a drug to substitute for self-control and their own efforts. That kind of miracle is not yet available, nor is it likely to be.

Expectations for magical cures are partly responsible for the growing frequency of medical malpractice suits. If a cure is not forthcoming, the patient assumes the doctor must be at fault. Sometimes he is at fault, but often too much is expected of him. So common have malpractice suits become that fear of them is adversely affecting the practice of medicine and is raising the cost of medical care. Today many doctors find it necessary to practice medicine defensively—that is, instead of concentrating only on the well-being of the patient, they must also order a large number of unnecessary test and examinations to answer questions they may be asked in court.

Scientists, engineers, and physicians cannot realistically hope that the favorable climate of 10 years ago will soon be restored. They can foster an improved climate, however, by persistently reminding the mass media and the public of the many limitations of science, technology, and medicine. We are neither witch doctors nor magicians.

Philip H. Abelson
Science 172 (June):989, 1971
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1. Mishima, S. and D. M. Maurice, The Effect of Normal Evaporation on the Eye, Exp. Eye Res., 1:46, 1961.
2. Bahr, Gunnar, Measurement of the Effect of Solutions of Different Osmotic Pressure on the Thickness of the Living Cornea, Trans. of Ophthal. Soc. U.K., 68:515, 1949.

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# Nixon-Kennedy Cancer Plans Fuse

The politicization of cancer took another step this month when President Nixon submitted legislation to set up a "cancer-cure program: at the National Institutes of Health but with a director reporting directly to him rather than to the head of NIH. Mr. Nixon's announcement was viewed as a political co-option of Sen. Edward Kennedy's autonomous "national cancer authority" proposal, which was on the verge of being reported out of committee. The two measures' remarkable similarity shows the effects of compromise negotiations between the Senator and HEW Secretary Elliot Richardson.

Although Mr. Nixon says the program will be "within" NIH, observers quickly discerned —and Richardson later confirmed to MWN —that it would be equal in rank to NIH and FDA. Thus it would absorb the NCI and be independent of NIH, at the same time being administratively tied to NIH and scientifically cooperating with the other institutes.

Many observers speculate that disturbing the makeup of NIH could signal the beginning of its breakup. Although the Administration has tried valiantly to portray the cancer-cure program as a part of the agency, under it NCI would no longer be equal in stature to the eight other NIH arms. Its budget would be made up separately and its grants and contracts would no longer have to be approved by an advisory council.

Other institutes—especially Heart and Lung—seem uptight about the impending change. If Heart and Lung can't compete to its satisfaction for funds within the NIH framework, its outside supporters may agitate for separate status too.

The director of Mr. Nixon's cancer program would be appointed by the President himself, subject to Senate confirmation. Richardson says this director (not yet chosen) "will not report to me, but directly to the President through the Office of Science and Technology." The present NCI director, Dr. Carl G. Baker, would become deputy director.

The reaction from Kennedy's office was swift but mixed. The Senator's health subcommittee immediately halted final processing of his bill, S. 34, and scheduled hearings on Mr. Nixon's proposal next week. A Kennedy spokesman says the President's bill "exceeded anything discussed between the Senator and Richardson." But he admits the two camps were "very close."

Both sides agree on a separate agency, headed by a Presidential appointee to provide over-all coordination and direction for a "moonshot" cancer cure. A spokesman for Kennedy says the only big difference now between the two camps is whether the super-agency stays within HEW. "We still feel that a NASA-type organization separate from HEW is the best approach, and the Administration is going to have to prove its idea is better," he says. Richardson says the agency would definately stay within HEW. The only question, he adds, is whether it would remain in NIH.

Mr. Nixon's new plan differs sharply from the one he described in his health message January 22. He then proposed a program completely within NIH, with its director subordinate to the NIH chief and, in effect, providing a kind of high-visibility leadership for NCI. The shift developed after it became clear that Administration efforts to bottle up S. 34 in the Senate Labor and Public Welfare Committee had failed, thanks largely, the White House concedes, to lobbying headed by philanthropist Mary Lasker.

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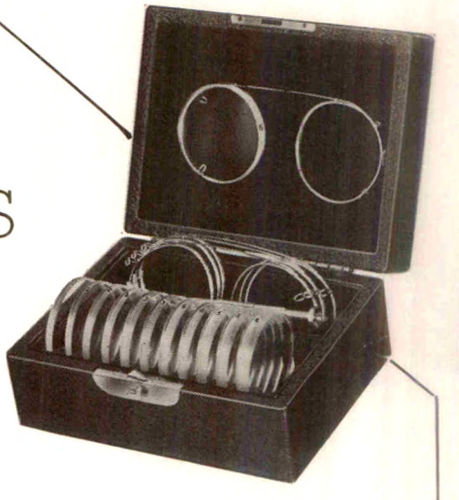
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|---|---|
| Afghanistan | 2 |
| Albania | 2 |
| Algeria | 3 |
| Argentina | 95 |
| Australia | 162 |
| Austria | 14 |
| Barbados | 2 |
| Belgium | 60 |
| Bermuda | 5 |
| Bolivia | 5 |
| Brazil | 111 |
| Bulgaria | 3 |
| Canada | 519 |
| Central African Rep. | 3 |
| Ceylon | 1 |
| Chile | 10 |
| China (Taiwan) | 18 |
| Colombia | 37 |
| Costa Rica | 7 |
| Cyprus | 4 |
| Czechoslovakia | 14 |
| Denmark | 46 |
| Dominican Republic | 5 |
| Ecuador | 8 |
| El Salvador | 5 |
| Ethiopia | 2 |
| Finland | 74 |
| France, incl. Monaco | 143 |
| Gambia | 1 |
| Germany, incl. Saar | 119 |
| Ghana | 2 |
| Great Britain | 299 |
| Greece | 93 |
| Guatemala | 6 |
| Haiti | 2 |
| Hong Kong | 8 |
| Hungary | 18 |
| Iceland | 3 |
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| Indonesia | 8 |
| Iran | 17 |
| Iraq | 8 |
| Ireland | 16 |
| Israel | 80 |
| Italy | 143 |
| Jamaica | 2 |
| Japan | 559 |
| Jordan | 3 |
| Kenya | 3 |
| Korea | 36 |
| Lebanon | 25 |
| Libya | 4 |
| Luxembourg | 1 |
| Malawi | 1 |
| Malaysia | 2 |
| Mali | 1 |
| Malta | 2 |
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| Morocco | 2 |
| Nepal | 1 |
| Netherlands | 145 |
| New Guinea | 1 |
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| Paraguay | 5 |
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| Rumania | 15 |
| Saudi Arabia | 11 |
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| Sudan | 3 |
| Surinam | 2 |
| Switzerland | 49 |
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| Tonga Islands | 1 |
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| Maryland—263 | |
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| Michigan—321 | |
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| Missouri—208 | |
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| Nebraska—48 | |
| Nevada—26 | |
| New Hampshire—19 | |
| New Jersey—310 | |
| New Mexico—35 | |
| New York—1138 | |
| North Carolina—143 | |
| North Dakota—19 | |
| Ohio—371 | |
| Oklahoma—67 | |
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| South Carolina—73 | |
| South Dakota—14 | |
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| Viet Nam | 3 |
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| Uruguay | 7 |
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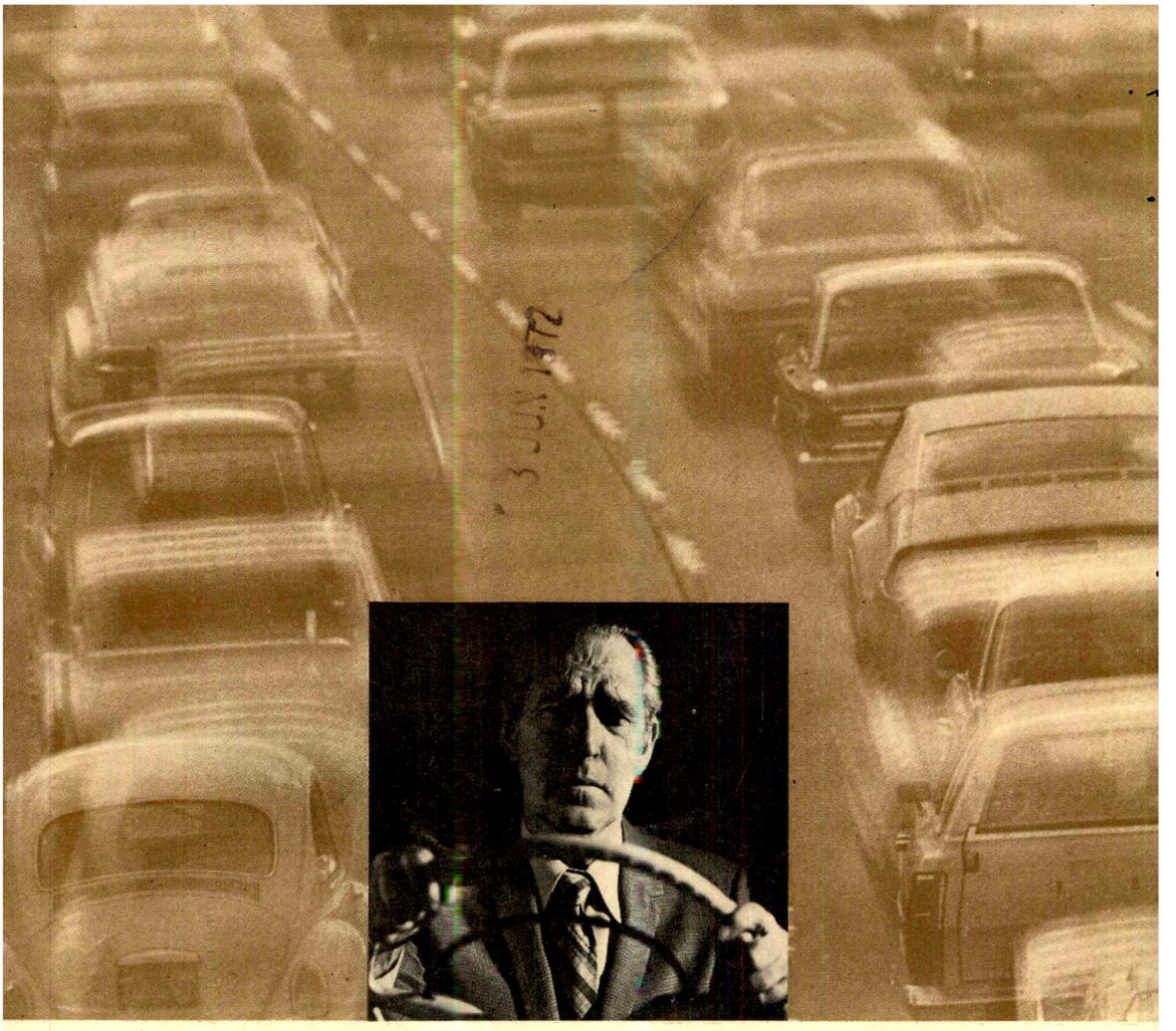

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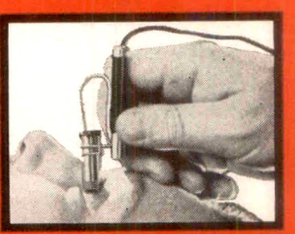
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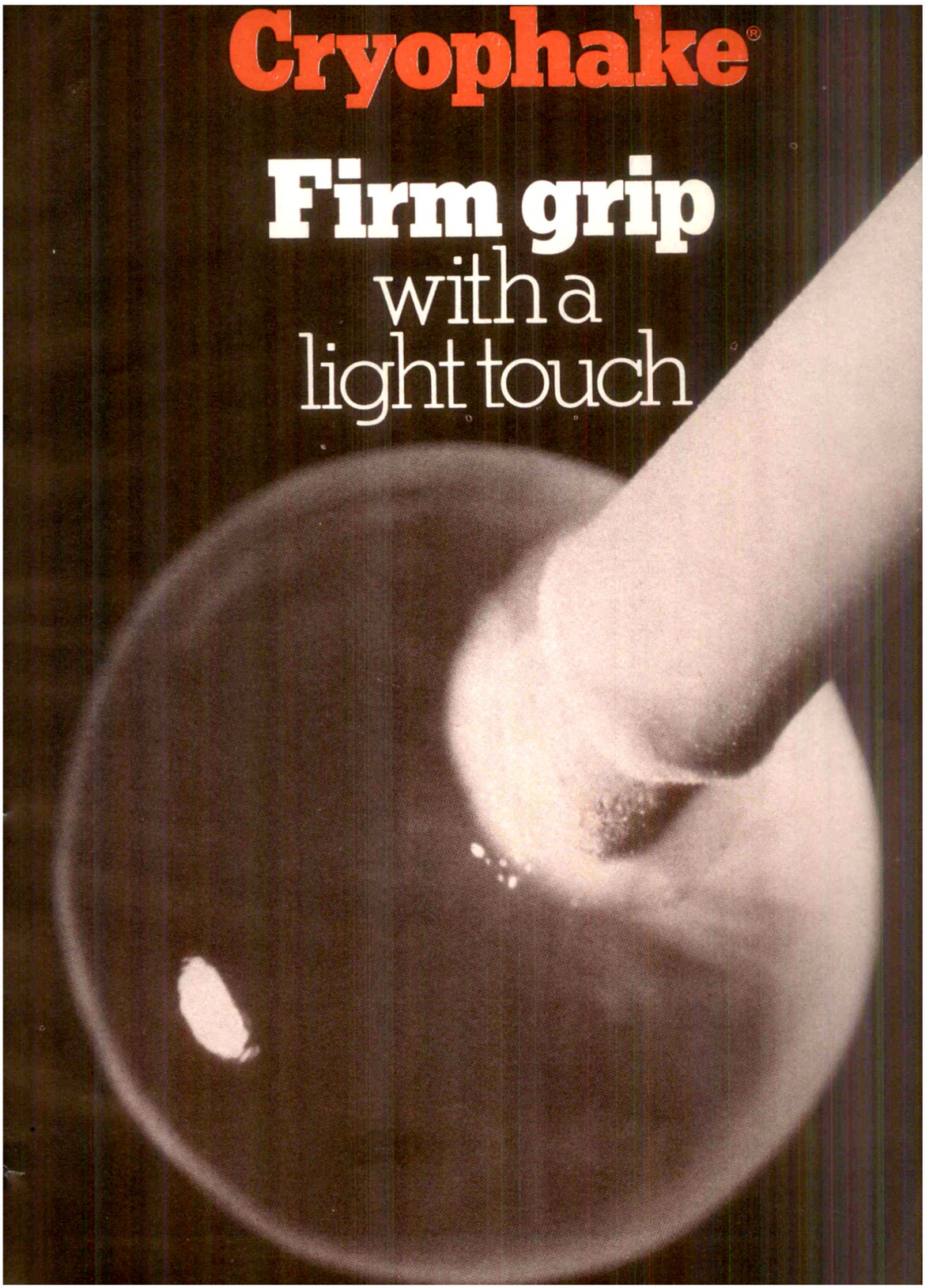
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**1.** Reynolds, A. M., Jr. and King, J. H. Jr.: Evaluation of a new Model Cryoextractor, E.E.N.T. Monthly. *48*:50-51 (Dec.) 1969. **2.** Haik, G. M., Ellis, G. S. and Pollard, J. B.: Selective Cryoextraction of the Cataractous Lens, Amer. J. Ophthal. *61*: 484-490 (March) 1966. **3.** Mattis, R. D., Brady, H. R., and Sugana, T.: Disposable Cryophake—Clinical Evaluation, Arch. Ophthal. *74*:787-791 (Dec.) 1965. **4.** Bellows, J. G.: The Mechanical Superiority and Advantages of Cryoextraction, Amer. J. Ophthal. *67*:1003-1009 (May) Part II, 1969. **5.** Cole, O. W. and Dunnigan, W. J.: Enzymatic Zonulolysis and Cryoextraction of Cataracts, Int. Surg. *50*:3 (Sept.) 1968.

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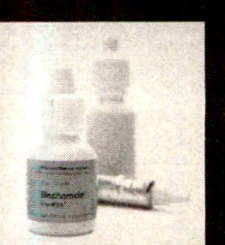
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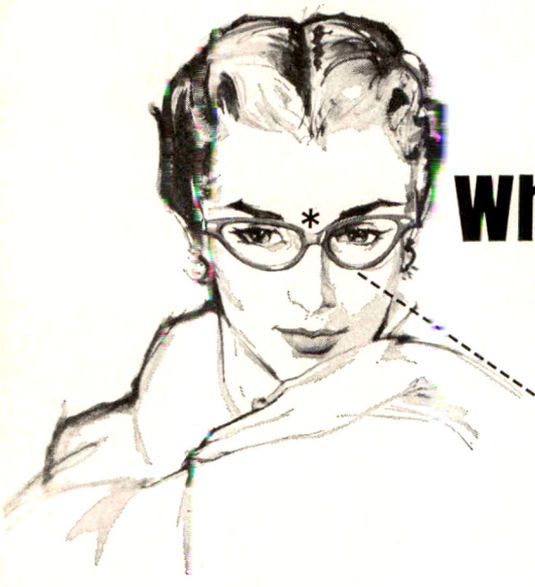
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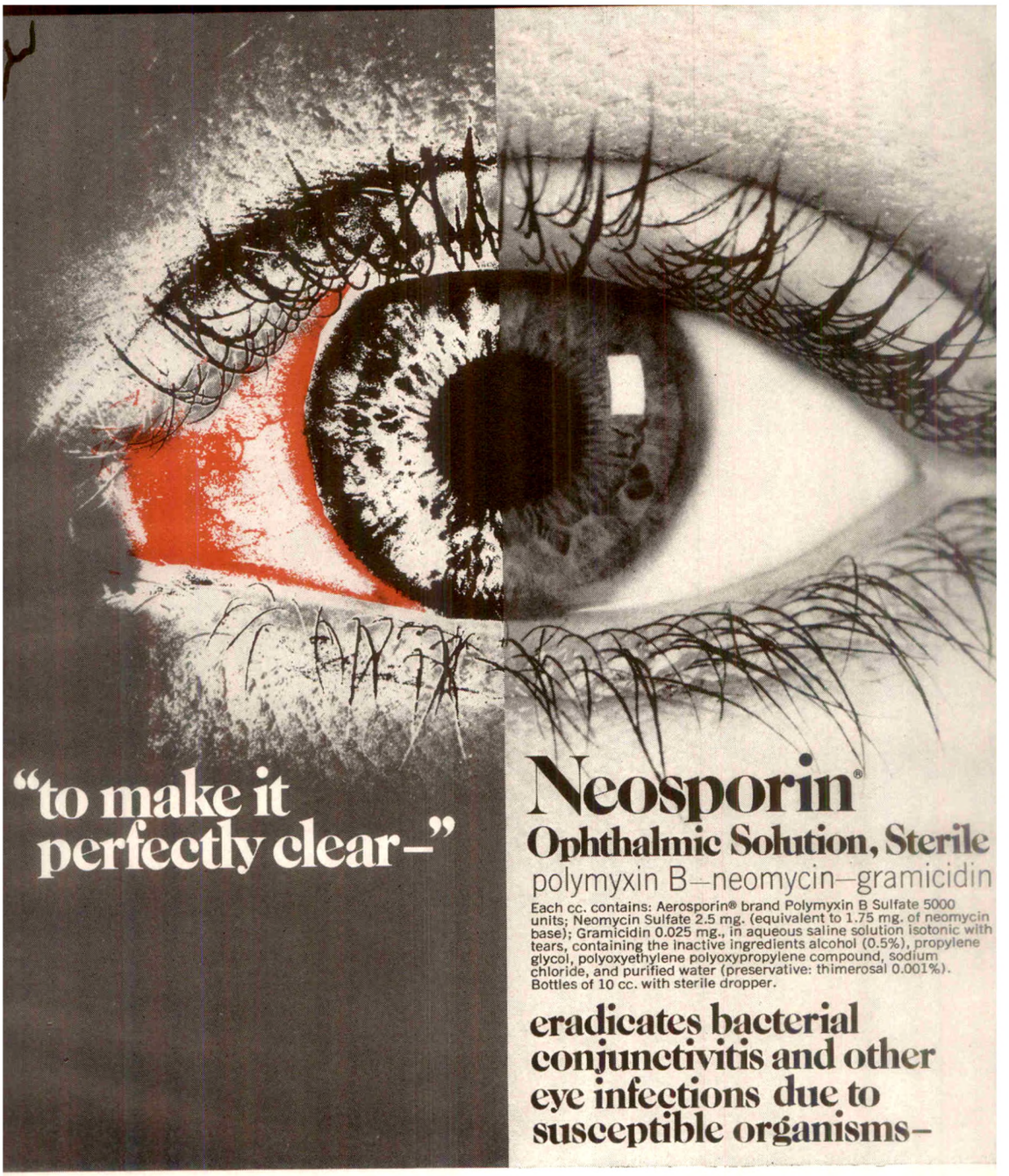
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Phosphate | MSD)

CONTRAINDICATIONS: DECADRON and NeoDECADRON should not be used in the presence of infectious tuberculous lesions of the eye, chickenpox, early acute herpes simplex, vaccinia, the early acute stages of most viral diseases of the cornea and conjunctiva, acute purulent untreated infections of the conjunctiva and lids, suspected ocular or aural fungal infection, perforated ear drum. Sensitivity to components is also a contraindication.

PRECAUTIONS: DECADRON: Like all adrenal corticosteroids, may sometimes mask, activate, or enhance incipient infection. Whenever possibility of infection exists, suitable antibiotic agents or a steroid-antibiotic preparation (such as NeoDECADRON) should be considered. If infections do not respond promptly, therapy should be discontinued until the infection has been adequately controlled by other measures.

Systemic side effects may occur with extensive use of steroids. Rarely, ocular herpes simplex has been reported in patients receiving adrenocortical steroids systemically or locally in the eye for other conditions.

As with other corticosteroids, increased intraocular tension can follow extended local use (1-2 weeks or more) of dexamethasone sodium phosphate. Since increased intraocular tension can lead to loss of vision, this possibility should be kept in mind and topical administration used only under adequate tonometric supervision, particularly in patients known to have glaucoma, or whose family history includes glaucoma.

In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids. Reports in the literature indicate that, rarely, protracted use of topical corticosteroids in the eye may be associated with the development of posterior subcapsular cataracts. Hereditary and degenerative eye diseases in general do not show any response to treatment with these preparations.

Stubborn cases of anterior segment eye disease may require systemic adrenocortical hormone therapy. When the deeper ocular structures are involved, systemic therapy is necessary.

NeoDECADRON: A few individuals may be sensitive to one or more of the components of NeoDECADRON. If any reaction indicating sensitivity is observed, discontinue use. Sensitivity to neomycin may occasionally develop, especially when it is applied to abraded skin. Some reports in the current literature point to an increase in the number of persons sensitive to neomycin.

Use of any antibiotic agent may result in overgrowth of fungi or other organisms not susceptible to the antibiotic, necessitating prompt medical attention for such new infections.

As the safety of topical steroids during pregnancy has not been confirmed, they should not be used for extended periods during pregnancy.

**For more detailed information, consult your MSD Representative or see the Direction Circular. Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa. 19486**

**MSD** MERCK SHARP & DOHME


soflens™
CONTACT LENS
(polymacon)




Conventional methods of fitting contact lenses do not apply to SOFLENS Contact Lenses (polymacon). For a detailed description of the fitting technique, refer to the SOFLENS Fitting Guide, copies of which are available from: SOFLENS Division, Bausch & Lomb Incorporated, Rochester, New York 14602.

**DESCRIPTION:** The SOFLENS Contact Lens (polymacon) is a hemispherical shell of approximately 13mm chord diameter and 0.1 to 1.0mm thickness. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The SOFLENS Care Kit is a package required for lens asepticizing, cleaning, and storage consisting of the following:

| | |
|---|---|
| SOFLENS Carrying Case | Cat. #140301 |
| SOFLENS Aseptor-Patient Unit | Cat. #140302 |
| SOFLENS Squeeze Bottle | Cat. #140304 |
| SOFLENS Salt Tablets | Cat. #140305 |
| SOFLENS Patient Instruction Book | Cat. #140300-100 |

**ACTIONS:** The SOFLENS Contact Lens (polymacon) absorbs water to 38.6% of its dry weight when equilibrated in normal saline solution. In its hydrated state a SOFLENS Contact Lens (polymacon) becomes soft and pliable. When placed on the human cornea the hydrated SOFLENS Contact Lens (polymacon) acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

**INDICATIONS:** SOFLENS Contact Lenses (polymacon) are indicated for the correction of visual acuity in persons with non-diseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

**CONTRAINDICATIONS:** SOFLENS Contact Lenses (polymacon) are contraindicated by the presence of any of the following conditions. (1) Acute and subacute inflammations of the anterior segment of the eye. (2) Any eye disease which affects the cornea or conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses. (6) Early stages of pregnancy.

**WARNINGS: Medicants and Eye Drops**—SOFLENS Contact Lens (polymacon) must be stored ONLY in normal saline solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by SOFLENS Contact Lens (polymacon) wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than normal saline may be used on SOFLENS when the lens is off the eye.
**Abrasions and Infections**—If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.
**Wearing Restrictions**—SOFLENS Contact Lenses (polymacon) should be removed before sleeping or swimming and in the presence of noxious and irritating vapors.
**Visual Blurring**—When visual blurring occurs the lens must be removed until the condition subsides.
**Lens Sanitation**—Patients who would not or could not adhere to recommended daily sanitary care of SOFLENS Contact Lenses (polymacon) should not be provided with them.

**PRECAUTIONS: Storage**—SOFLENS Contact Lenses (polymacon) must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be soaked in normal saline solution until it returns to a soft, supple state.
**Cleaning and Asepticizing**—SOFLENS Contact Lenses (polymacon) must be BOTH cleaned and asepticized daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. ASEPTICIZING with the SOFLENS Aseptor-Patient Unit has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the SOFLENS Carrying Case. Fresh normal saline must be prepared daily for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before asepticizing the lenses. If a SOFLENS Aseptor-Patient Unit is not available for asepticizing the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.
**Hygiene**—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.
**Fluorescein**—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

**ADVERSE REACTIONS:** Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline and wait until the lens moves freely before removing it. Clinical studies indicate visual blurring is experienced by less than 5% of SOFLENS Contact Lens (polymacon) wearers. Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

**DOSAGE AND ADMINISTRATION:** There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

| Day | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) |
|---|---|---|---|---|---|
| 1 | 3 | 1 | 3 | 1 | 3 |
| 2 | 3 | 1 | 3 | 1 | 3 |
| 3 | 4 | 1 | 4 | 1 | 4 |
| 4 | 4 | 1 | 4 | 1 | 4 |
| 5 | 6 | 1 | 6 | 1 | 4 |
| 6 | 6 | 1 | 6 | 1 | 4 |
| 7 | 8 | 1 | 8 | | |
| 8 | 8 | 1 | 8 | | |
| 9 | 8 | 1 | 8 | | |
| 10 | 10 | 1 | balance of the waking hours* | | |
| 11 | 12 | 1 | balance of the waking hours* | | |
| 12 | 14 | 1 | balance of the waking hours* | | |

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a SOFLENS Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

**HOW SUPPLIED:** Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the dioptric power (black for plus power lenses; red for minus) and the manufacturing lot number of the lens. To assure proper lens care and handling, each SOFLENS patient must be supplied with a complete SOFLENS Care Kit.

BAUSCH & LOMB
SOFLENS DIVISION

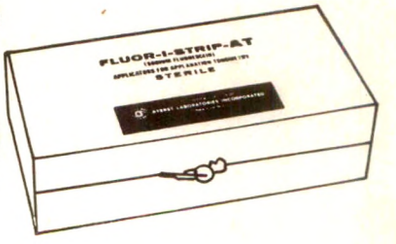


**When fitting contact lenses: to guard against the risk of infection inherent in the use of sodium fluorescein solutions, stain eyes with sterile Fluor-I-Strip-A.T. No excess fluorescein to stain the patient's face or clothing...water-proof grip to prevent staining of your fingers. Simply retract upper lid, apply dry orange tip of flexible applicator to the bulbar conjunctiva at the temporal side. For all these benefits: Specify Ayerst**





**FLUOR-I-STRIP®-A.T.**
**(sodium fluorescein)**
**STERILE OPHTHALMIC APPLICATORS.**

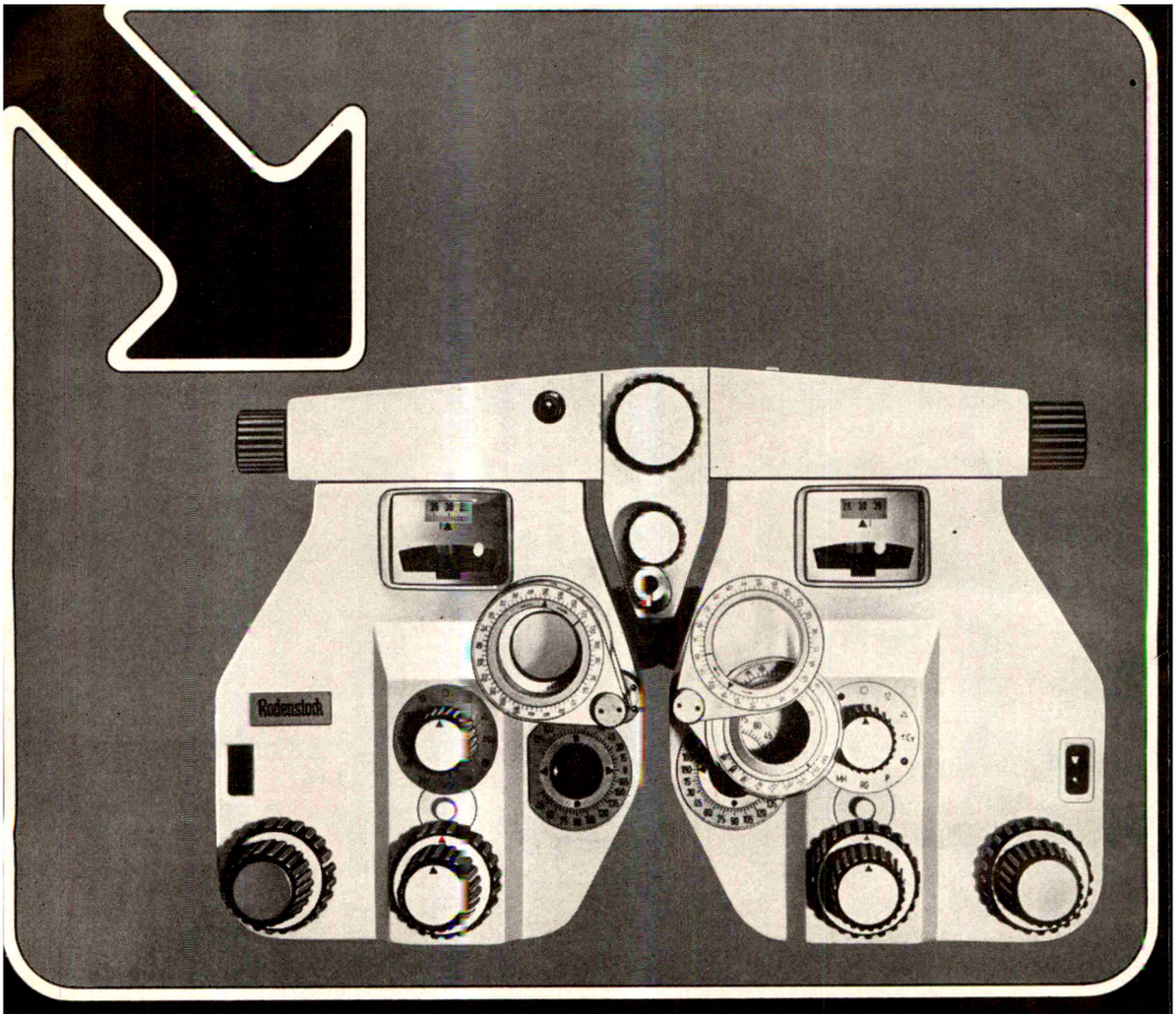



*Each applicator contains* not less than 1.0 mg. sodium fluorescein —provided by precise impregnation with a solution of sodium fluorescein and 0.5% chlorobutanol (chloral derivative), polysorbate 80, boric acid, potassium chloride, and sodium carbonate. *Supplied:* No. 1048—Boxes of 100 envelopes, each envelope containing 2 firm sterile applicators—one for each eye.

OPHTHALMOS DIVISION

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

7047




# Phoropter

- Power range sphs. −20·0 to +25·75 D cyls. −8·75 D
- Corneal vertex distances from 12 mm to 24 mm determined with accuracy
- Vertical height adjustment and independent P. D. adjustment
- Interchangeable cross cylinders
- Lenses anti-reflection coated and corrected curves
- Pilot lamp activated by forehead rest to ensure correct corneal distance
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- Angled tilt device for reading position
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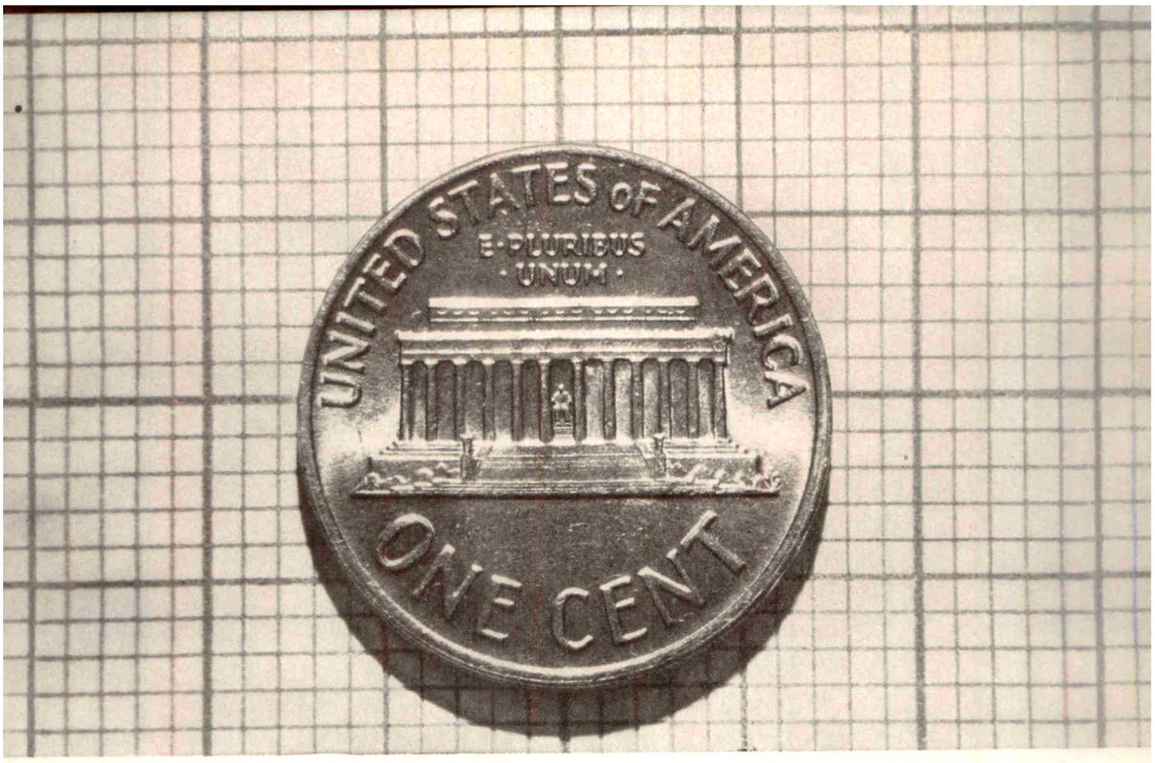
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# OpMi 6 lets you see a lot more than you'd expect... and gives you the widest field, too...

**55 mm at 3.6x,**
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At all magnifications the new OpMi 6 gives you the widest field of view of any operation microscope. And, within the field, the image quality is truly extraordinary. As you can see above, there is high resolution and contrast, and the graph paper demonstrates the perfectly flat field with no distortion edge-to-edge.

For all microsurgical disciplines, the OpMi 6 offers you features unmatched anywhere: **(1)** The precisely controlled zoom system–fully motorized, 1:5, constant angular zoom. Easy to get the precise magnification you want at any microscope orientation you want—vertical, horizontal or anywhere in between; **(2)** The unique motorized focusing along the optical axis regardless of the angle of the microscope; **(3)** The brilliant and uniform co-axial illumination—external slit and homogeneous illumination also available; **(4)** The working distance is adjustable—from 4" to 16" in steps of 1"—and up to 7' (to carry things to an extreme); **(5)** All the famous Zeiss accessories—the Beam Splitter for photography, television, and supplementary viewing systems through the microscope optics, high-eyepoint eyepieces for spectacle wearers; much more.

Ask anyone who has seen this microscope what they think of it. Better yet, ask us. Write or call Carl Zeiss, Inc., 444 Fifth Ave., New York, N. Y. 10018. (212) 736-6070.

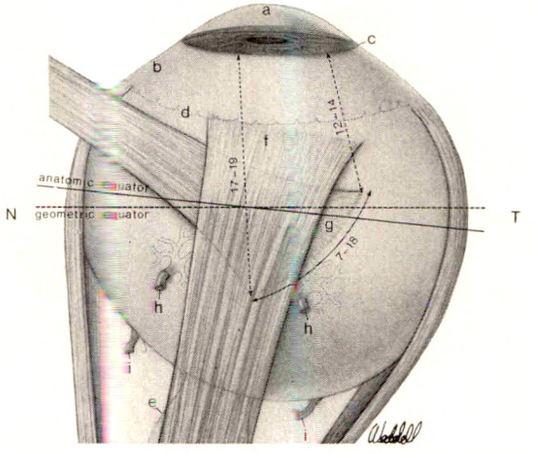
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# A Graphic Guide to the Structure and Function of the Visual Apparatus




## Hogan, Alvarado & Weddell: HISTOLOGY OF THE HUMAN EYE

*By **Michael J. Hogan,** M.D., Professor and Chairman, Department of Ophthalmology, and Research Associate, with **Jorge A. Alvarado,** A.B. and **Joan Esperson Weddell.** All of the Francis I. Proctor Foundation for Research in Ophthalmology, Univ. of Calif., San Francisco. 687 pp. 503 figs. $34.00. August, 1971. **Slide Supplement:** About $110.00. Just Ready.*

**Using remarkably clear illustrations** and detailed text descriptions, the authors of this definitive and unified new work fully describe the physiology, embryology, gross and microscopic anatomy of the human eye.

**Each component** of the ocular apparatus is systematically discussed and examined by light and electron microscopy, and findings are coherently summarized in beautiful three-dimensional drawings that depict the organization of the tissues.

**Individual chapters** are devoted to each structural component of the eye, from the limbus to the optic nerve. A supplementary series of 200 meticulously prepared 35mm slides of illustrations from the book is also available. Ideally suited for individual or classroom instruction, this excellent visual aid may be purchased separately, or used as a supplement to the text itself.

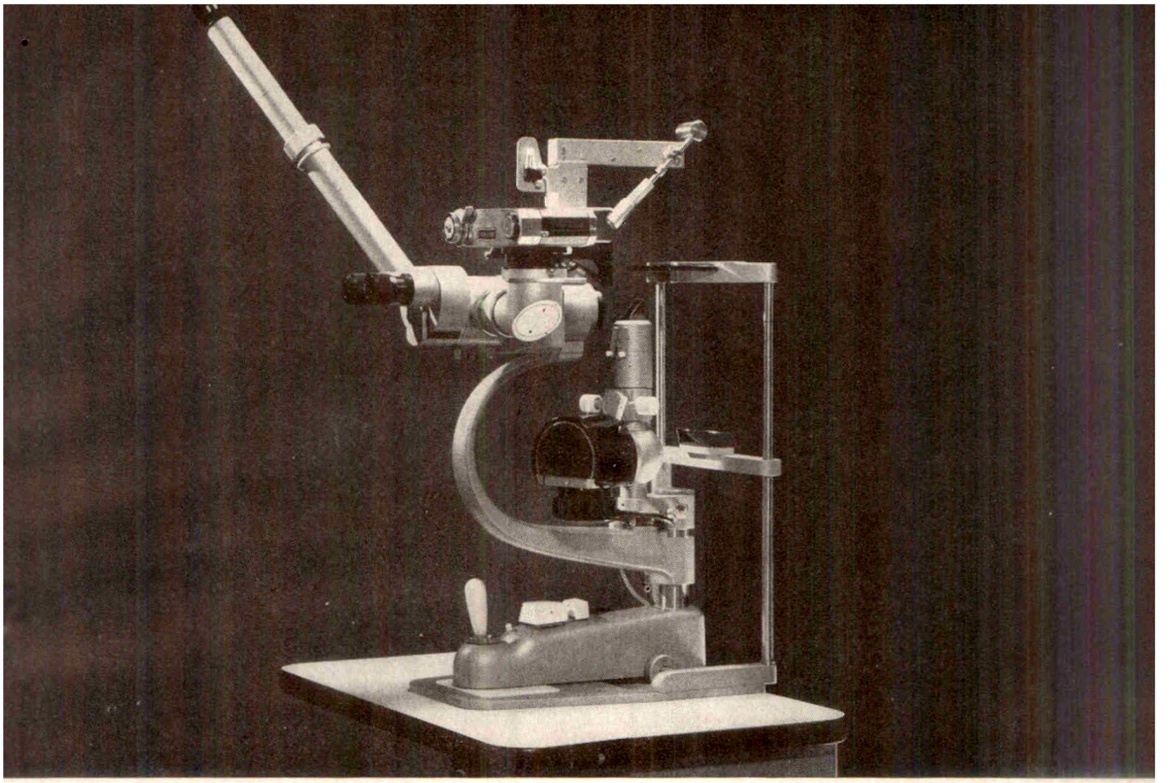
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**West Washington Square, Philadelphia, Pa. 19105**

Please send me: ☐ Hogan, Alvarado & Weddell: HISTOLOGY OF THE HUMAN EYE, $34.00.
☐ Easy Pay Plan ☐ SLIDE SUPPLEMENT: 200 35mm slide set, About $110.00. Ready October, 1971.

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Slit Lamp PE/E with Hruby lens, fixation device, applanation tonometer, beam-splitter, observation tube and camera.

# Why a Zeiss Slit Lamp? Because you get precisely what you pay for.

Precisely means the high resolution that has made Zeiss optics world-famous, and the precision operation that has made Zeiss engineering synonymous with craftsmanship. And, to make sure that the slit lamp you buy will be tailored precisely to you and your work, you can choose from a range of instruments and features unmatched by anyone. There's no reason all slit lamps should be alike (after all, all people aren't), so with Zeiss, even before you consider accessories, your choice is a wide one. For your convenience, we have:

**4 basic models**—manual and motorized, step-wise and zoom. The step-wise magnification system is from 6x to 40x (the widest range of any slit lamp from anyone), the zoom is 8x to 40x. They're called the SM/M, the PM/M, the PE/E, and, of course, the famous Photo-Slit Lamp, the ultimate in sophistication. Standard on the Photo-Slit Lamp, and available also on the other three models, is an extra-long working distance to facilitate surgical intervention.

**The unique Galilean observation system**—it allows the famous Zeiss beam-splitter (used on our Operation Microscopes) to be inserted, letting you attach observation tubes and still, cine, and television cameras—invaluable aids for consultation or teaching purposes—all operating directly through the optics of the microscope. And because it is telecentric, this system lets you work with eyes relaxed, focused on infinity, *sans* strain. It quite literally means fewer headaches.

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**High-eyepoint eyepieces**—for physicians who must wear corrective lenses, these eyepieces offer the same wide field of view enjoyed by non-eyeglass wearers.

**Ease-of-handling**—these light-in-weight instruments are easy to use on a refraction unit or a table, whether you're left- or right-handed, tall or short, or have any kind of special requirements.

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# Coals hot Steak rare Eyes raw

Windblown smoke and heat from cookouts make eyes burn and water. Vasocon-A relieves the discomfort. Long-acting vasoconstrictor-decongestant, antihistamine. Reduces burning and itching. Good after contact lens insertion and removal, too.

CAUTION: Federal law prohibits dispensing without prescription. See package insert before prescribing.

COMPOSITION: Naphazoline HCL, 0.05%; antazoline phosphate, 0.5%; boric acid, 1.2%; sodium carbonate anhydrous; sodium chloride; phenylmercuric acetate (preservative) 0.002%.

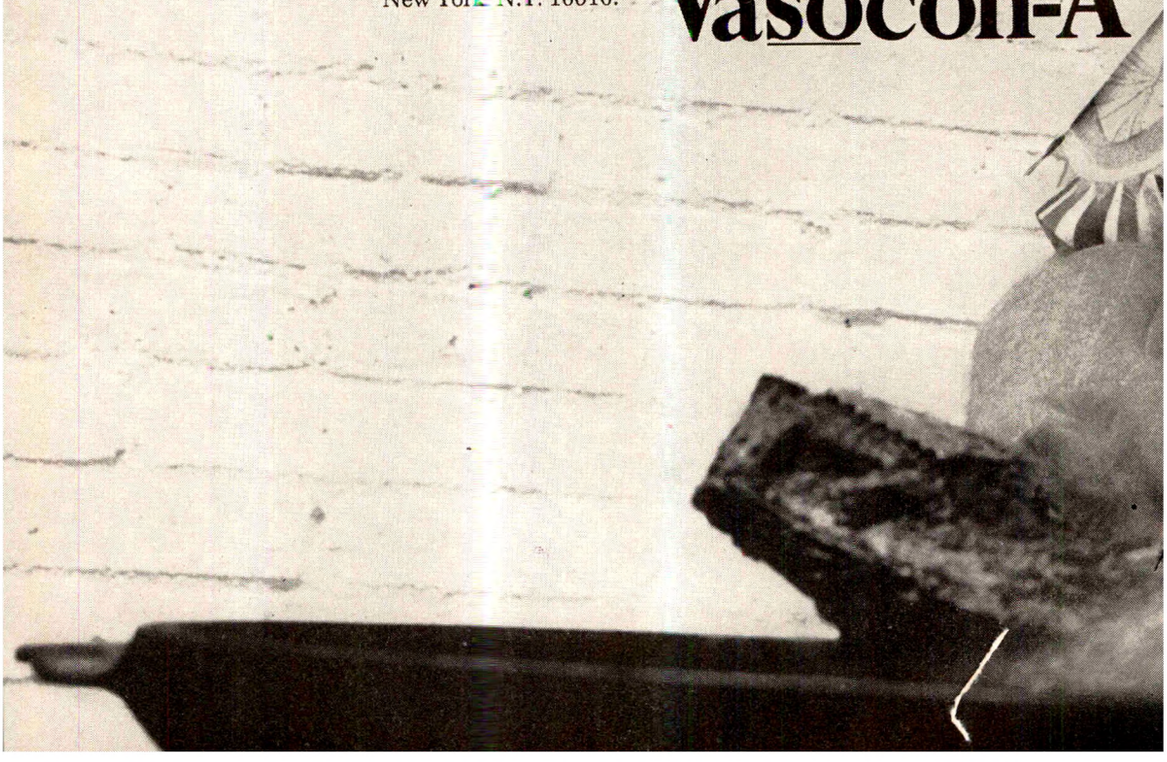
SIDE EFFECTS: Except for transitory stinging, side effects have rarely been encountered.

CONTRAINDICATIONS: Should not be used by patients with narrow angle glaucoma. If irritation persists or increases, patient should be advised to discontinue use and return to physician.

SUPPLIED: 15 cc plastic dropper-tip vials.

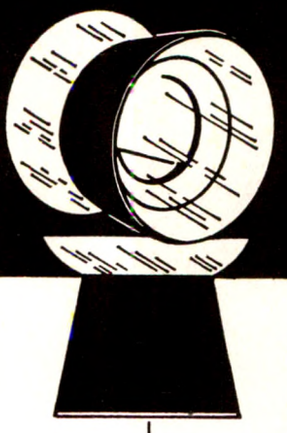
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**Vasocon-A®**




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# MURO
# GONIO-GEL



A STERILE GEL OF METHYLCELLULOSE 4000 cps 2.5%
Preservatives: Methylparaben and Propylparaben

## VALUABLE FOR BONDING OF GONIOSCOPIC PRISMS TO THE CORNEA

- Simplifies gonioscopy in upright and recumbent positions
- Reduces fluid spillage
- Helps maintain a tight lens fit
- Index of refraction 1.336

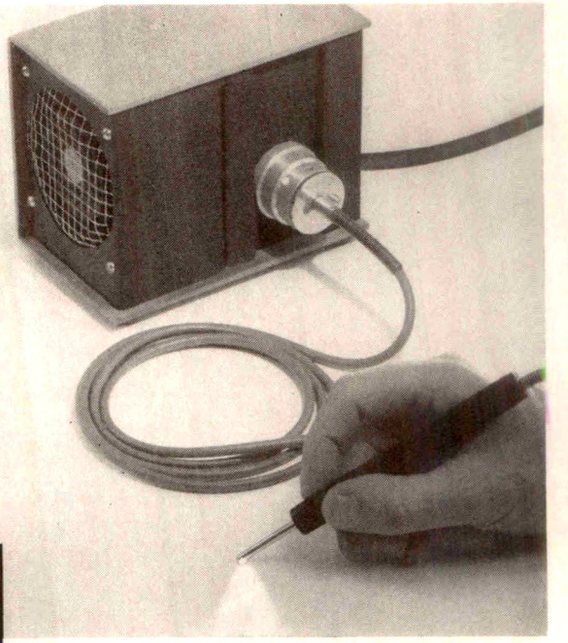



Apply small amount of Gel to inner surface of Gonio lens.
Available in ⅛ ounce ophthalmic tubes.

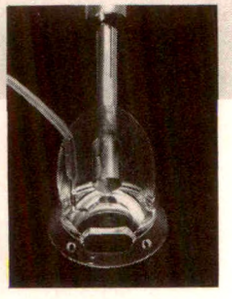
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*Diagnostic and Surgical High Intensity Transilluminator*

Extremely flexible fiber optic bundle transmits strong, cold light to a straight or right angle probe or to special lenses for gonioscopy and goniotomy







The High Intensity Transilluminator is particularly useful in the study and management of the following conditions:

**Retinal Detachment**-Determining the shape and position of large choroidal structures such as vortex veins and long ciliary nerves and arteries. This permits the surgeon to avoid these structures with diathermy or perforation.

**Intraocular Foreign Bodies**-Detecting intraocular foreign bodies located close to the ocular wall, even if the transparent media are cloudy.

**Uveal Tumors**-Examining the posterior segment (with or without vitreous hemorrhage) for the presence of a tumor.

**Gonioscopy and Goniotomy**-Direct, illuminated viewing of the chamber angle. The Transilluminator provides internal, retro-illumination for the gonioscopy lens #MW54 (with additional clip-over lens for higher magnification) and the Goniotomy Lens #MW52A (with scleral rim and suturing holes).

The powerful and cold light of the Transilluminator is also suitable for illumination of the anterior segment and illumination of the surgical field when operating near the globe's posterior pole.

**MEDICAL INSTRUMENT RESEARCH ASSOCIATES INC.**
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A

*Please send the following instruments:*

☐ #OS-550 High Intensity Transilluminator, complete with light source, fiber optic bundle with handle and right angle prism @ $170.
☐ #OS-551 Same as above, 220 volt @ $190.
☐ #MW54 Prismatic Gonioscopy Lens with additional clip-over lens @ $125.
☐ #MW52A Prismatic Goniotomy Lens with scleral rim and suturing holes. Used with #OS-553 @ $100.
☐ #OS-553 Fiber Optic Bundle without handle @ $35.

*Please send descriptive literature on:*

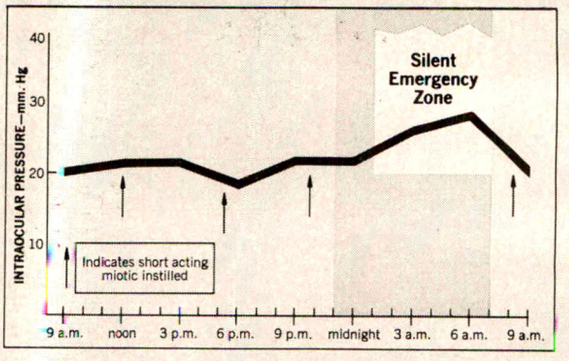
☐ Light Coagulator MF1000
☐ Implants for Retinal Detachment Surgery
☐ S P Ophthalmoscope Stand OS-150
☐ S P Ophthalmoscope OS-700
☐ Transistor Diathermy TR2000
☐ Low Vacuum Diagnostic and Surgical Contact Lenses

Name _____ Title _____
Hospital or Clinic _____
Address _____
City _____ State _____
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# Not more potent, but longer acting...*

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

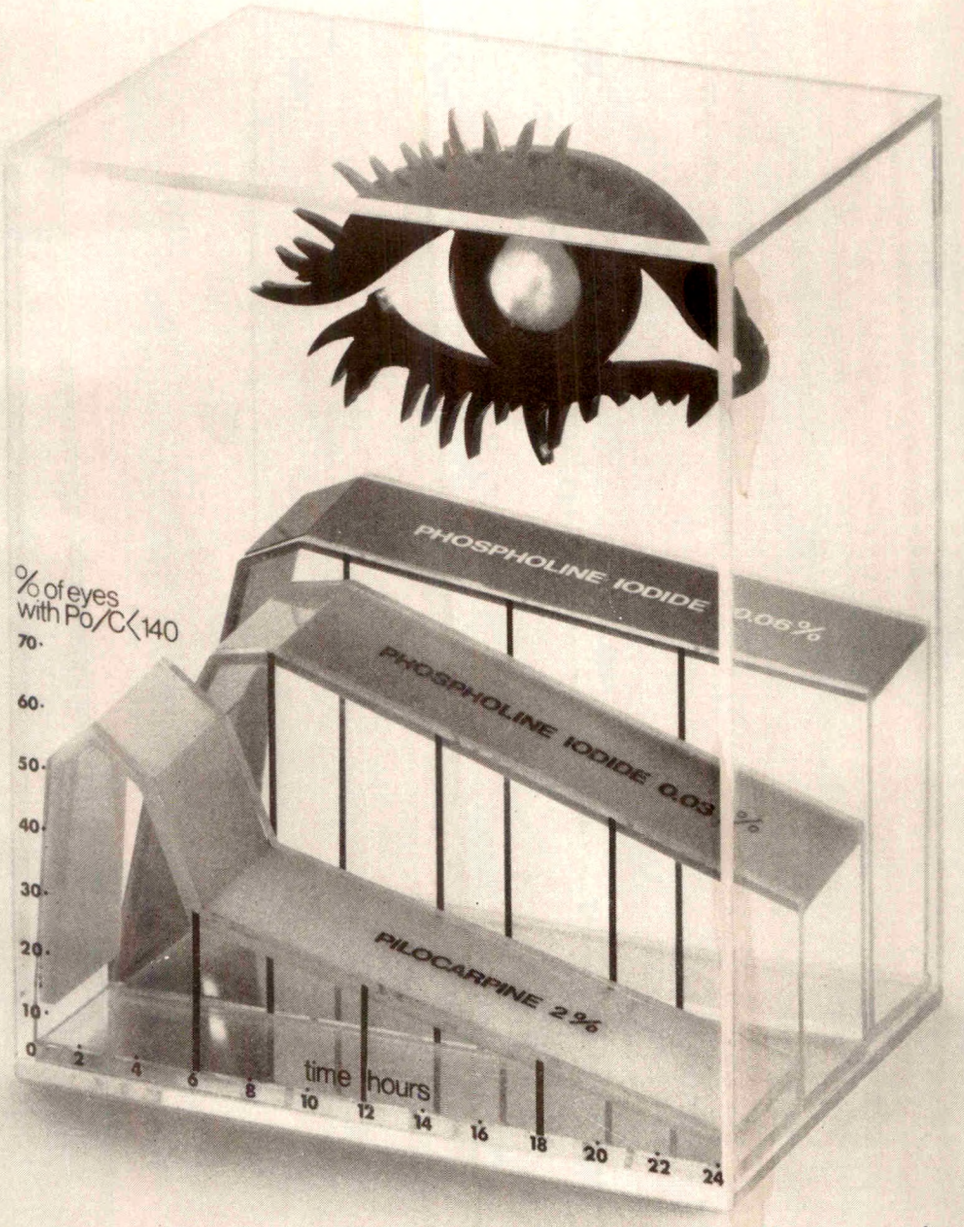



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25% —when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

## for 24 hour control in chronic simple (open-angle) glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, brow-ache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

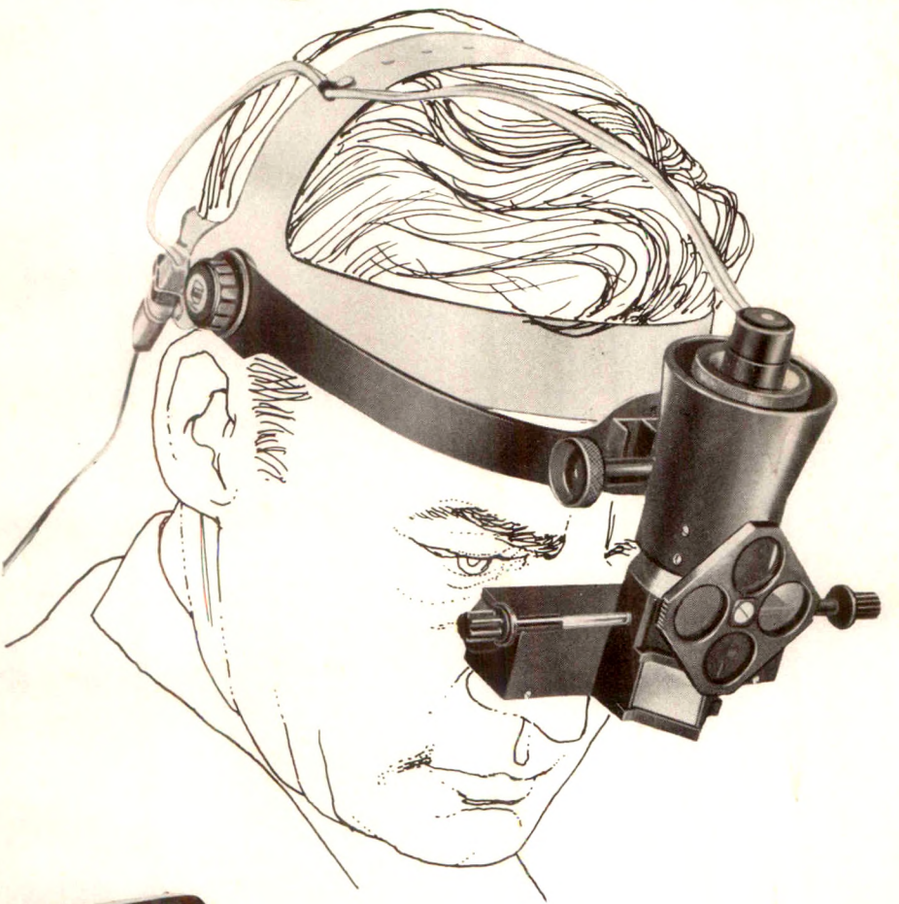
*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

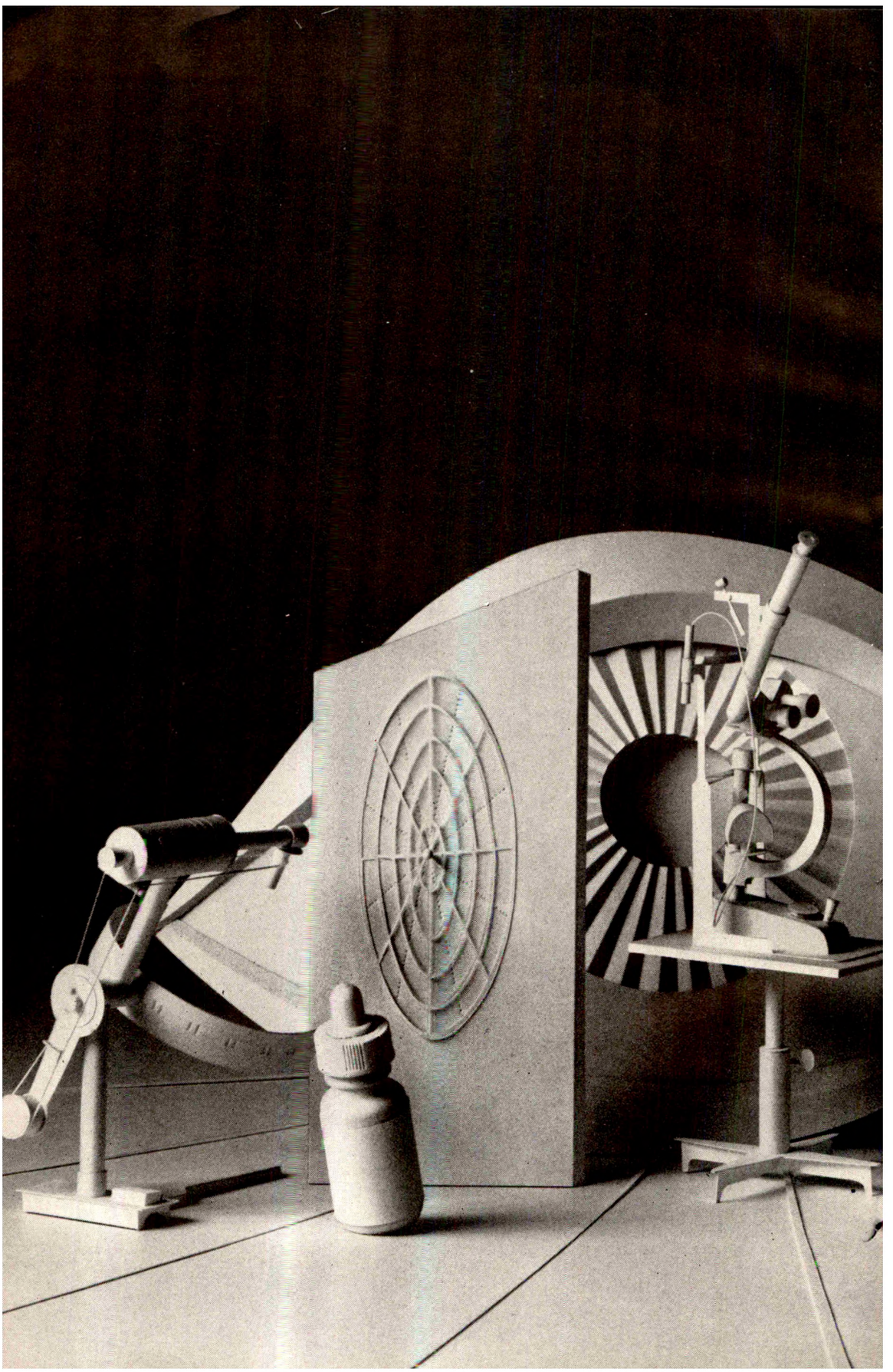
# The Fison indirect ophthalmoscope is an integrated, versatile, system

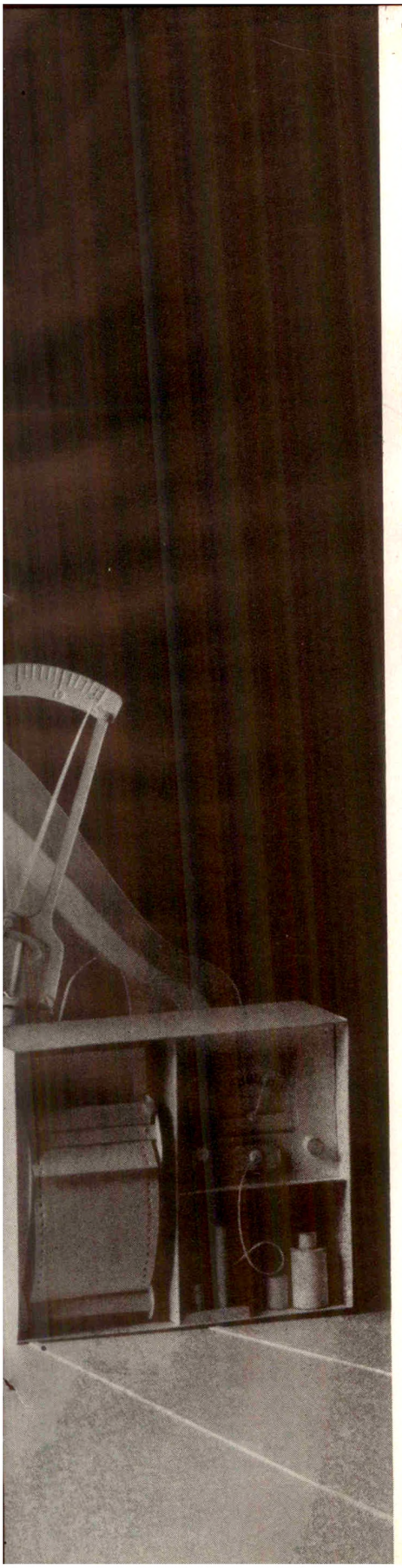




The Fison binocular ophthalmoscope offers as standard many attachments usually considered as extras ; plus the unique 'bi-mirror' which allows consultation with or instruction of two extra observers, able to view the fundus simultaneously from left and right. The high intensity light source is venturi-section cooled for maximum wearer comfort while the newly-designed vision system combines optical stability with minimum weight. Fully stereoscopic viewing through automatically-aligning lenses in an adjustable P.D. system gives optimum depth perception. The integral but detachable filter wheel is supplied fitted with cobalt and red-free filters ; provision is made for incorporation of special colour filters for specific study and research work. The tough, smart carrying case has a fitted, removable transformer, accessory compartment and pocket for detachment charts and case notes.

**KEELER OPTICAL PRODUCTS INC · 456 PARKWAY, BROOMALL, PA. 19008**





# When epinephrine is indicated for the management of chronic simple (open-angle) glaucoma

# Ayerst Epitrate® BRAND OF epinephrine bitartrate

BRIEF SUMMARY

*(For full prescribing information, see package circular.)*

**Epitrate**® (epinephrine bitartrate)

***For management of chronic simple (open-angle) glaucoma***

**Description:** A sterile aqueous solution of levorotatory epinephrine bitartrate 2% (equivalent to 1.1% base), it is stable, retains its potency throughout use, and requires no refrigeration. It has a low surface tension.

**Action:** Intraocular pressure is lowered by reducing the rate of aqueous formation. Improvement in outflow facility is also observed in certain cases following prolonged therapy.

**Indications:** Useful in management of chronic simple (open-angle) glaucoma, either alone or in combination with miotics. In selected cases, it may also be used with carbonic anhydrase inhibitors.

**Contraindications:** Prior to peripheral iridectomy, an epinephrine preparation is contraindicated in eyes that are capable of angle closure since its relatively weak mydriatic action may, nevertheless, precipitate angle block. Gonioscopy should be carried out on all patients before initiating therapy.

**Warnings:** Topical use of epinephrine in any form should be interrupted prior to general anesthesia with certain anesthetics such as cyclopropane or halothane which sensitize the myocardium to sympathomimetics.

**Precautions:** EPITRATE (epinephrine bitartrate) should be used with caution in the presence of hypertension, diabetes, hyperthyroidism, heart disease, and cerebral arteriosclerosis because of the possibility of systemic action.

**Adverse Reactions:** As with other epinephrine solutions, transitory stinging on initial instillation may be expected. Headache or browache frequently occur on beginning EPITRATE therapy, but usually diminish as treatment is continued. Conjunctival allergy occurs occasionally. Pigmentary deposits in the lids, conjunctiva or cornea may occur after prolonged use of epinephrine eyedrops. In rare cases, maculopathy with a central scotoma may result from the use of topical epinephrine in aphakic patients; prompt reversal generally follows discontinuance of the drug. Systemic effects have occasionally been reported, such as: palpitation, tachycardia, extrasystoles, hypertension, trembling, sweating, and pallor.

**Dosage and Administration:** 1 drop, with frequency of instillation being individualized, from every two or three days to twice daily. More frequent instillation than one drop four times daily does not usually elicit any further improvement in therapeutic response.

**How Supplied:** No. 1015–EPITRATE–ophthalmic solution of epinephrine bitartrate 2% (equivalent to 1.1% base). [Also contains chlorobutanol (chloral derivative) 0.5%, methylaminoaceto pyrocatechol HCl, sodium bisulfite, sodium chloride, polyoxypropylene-polyoxyethylene-diol, and disodium edetate.] Package containing 7.5 cc. bottle with separate dropper-screw cap attachment.

The Ophthalmos Division
**AYERST LABORATORIES**
New York, N.Y. 10017

7141

# COVELLI CRYOEXTRACTOR

FOR CATARACTS

*Now available...*



ACTUAL SIZE

## NO MORE ACCIDENTAL ADHESIONS!

ONCE YOU GRASP THE LENS, AT NO TIME DOES THE IRIS OR ANY OTHER TISSUE ADHERE TO THE PROBE, EVEN WHEN THERE IS DIRECT CONTACT!. THIS EXCEPTIONAL ADVANTAGE IS DUE TO ITS SPECIALLY DESIGNED TIP.

OTHER IMPORTANT ADVANTAGES:

- Thin tip (2.75 mm.) with special shape for better visibility.
- Light weight (11 g.) Just like your ball pen.
- Heat-resistant, so it can be autoclaved repeatedly.
- Durable, it can be used a great number of times.
- Rechargeable, uses gas *"FREON" 12; commercially available.
- Low price.

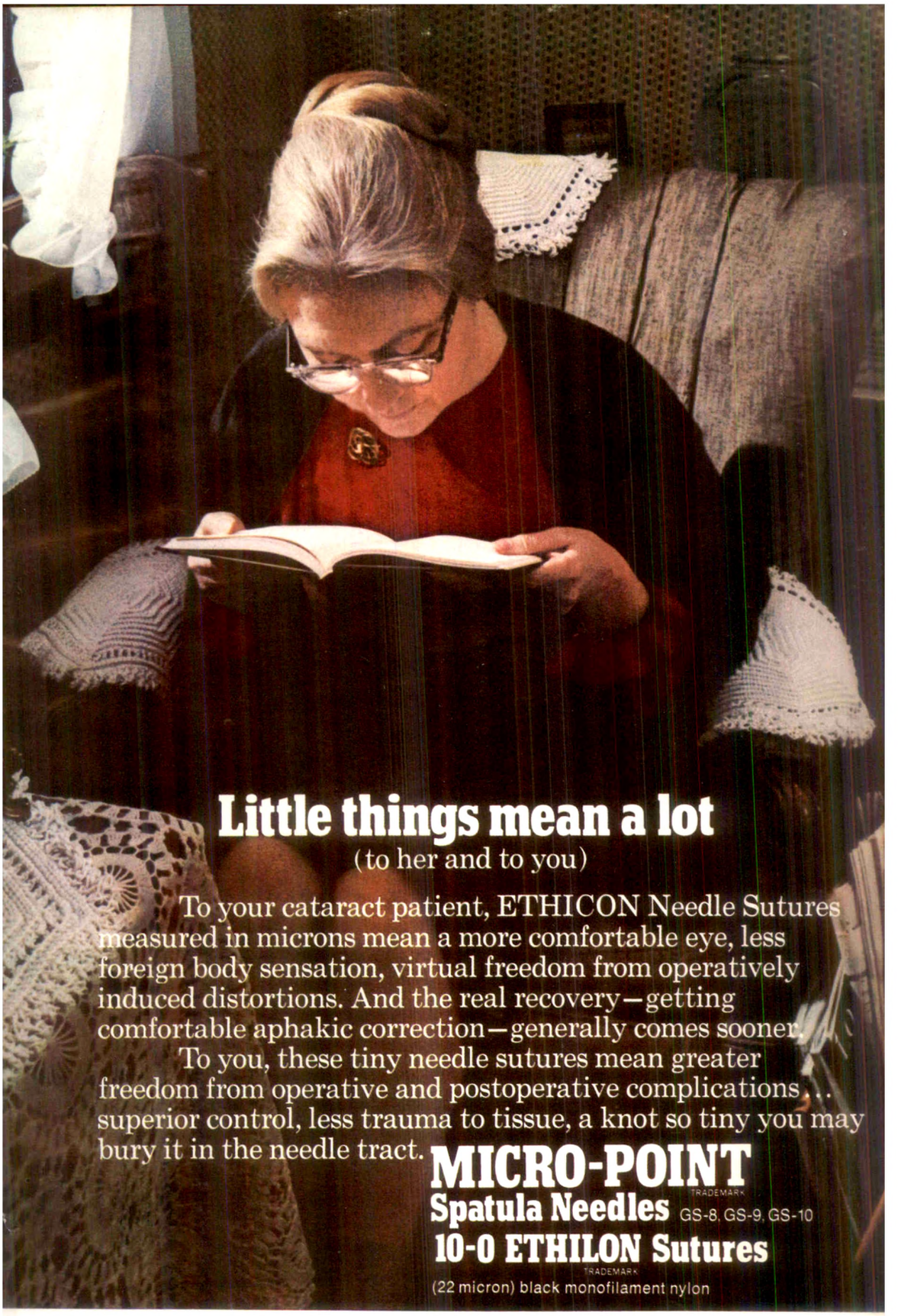
Ref. : Covelli B. Am. J. Ophth., 69:3, 1970
Presented at the VII Pan-Am. Congr. Ophth., Bogota. 1971

*Reg'd Trademark E. I. DuPont

F. D. Gillespie, M. D.
1205 Market Street
Parkersburg, West Virginia.

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ADDITIONAL LITERATURE

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# Little things mean a lot

(to her and to you)

To your cataract patient, ETHICON Needle Sutures measured in microns mean a more comfortable eye, less foreign body sensation, virtual freedom from operatively induced distortions. And the real recovery—getting comfortable aphakic correction—generally comes sooner.

To you, these tiny needle sutures mean greater freedom from operative and postoperative complications... superior control, less trauma to tissue, a knot so tiny you may bury it in the needle tract.

**MICRO-POINT**™
**Spatula Needles** GS-8, GS-9, GS-10
**10-0 ETHILON**™ **Sutures**
(22 micron) black monofilament nylon

totally responsible leadership **ETHICON**

# Little needle, little suture. Little trauma.

A finer mini-suture than has ever before been available, ETHILON 10-0 Monofilament Nylon is made to be left in place indefinitely. Photo shows ETHILON Nylon Sutures in the eye. (MICRO-POINT Spatula Needle GS-10 was used. Arc over eye is a reflection of camera light.)

Photo courtesy of Richard C. Troutman, M.D., F.A.C.S., State University of New York, Downstate Medical Center.

**MICRO-POINT** TRADEMARK
**Spatula Needles** GS-8, GS-9, GS-10
**10-0 ETHILON Sutures** TRADEMARK
(22 micron) black monofilament nylon

Sharper, flatter, smaller, the MICRO-POINT Spatula Needle measures only 0.203 mm., compared to 0.330 mm. for a conventional reverse cutting ophthalmic needle...makes for easier splitting of sclera, minimal trauma.

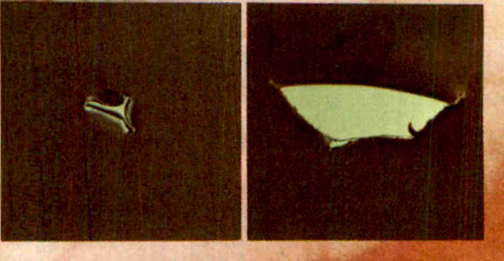


Photo shows the small hole the MICRO-POINT Spatula Needle makes in test material (left), compared to the hole made by conventional reverse cutting needle (right).

totally responsible leadership ETHICON

# A singular new antibiotic for the eye that works the way you think it should

## GARAMYCIN® brand of GENTAMICIN SULFATE OPHTHALMIC SOLUTION/OINTMENT



Each cc. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

## You think it should have a wide antibacterial spectrum

GARAMYCIN's wide range of antibacterial action is equal to the spectrum commonly prescribed in the combinations of neomycin, polymyxin and bacitracin or gramicidin in the treatment of external eye infections due to susceptible organisms. It has activity against a wide variety of both gram-positive and gram-negative organisms, including the "difficult" ones—*Pseudomonas aeruginosa* strains and Proteus.

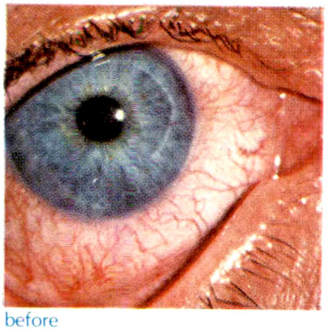
## You think it should be a single entity antibiotic

GARAMYCIN is a single entity antibiotic with a low incidence of sensitization or resistance*—can be used repeatedly with continued effectiveness, less concern about allergic potential (*Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.)

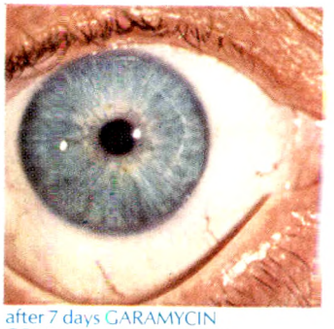
## You think it should be clinically effective

GARAMYCIN OPHTHALMIC has been described as appearing to be "...an antibiotic of choice for the initial treatment of external ocular infections."[1] It has "proved highly effective...for a wide variety of common bacterial eye infections..."[2] (due to susceptible organisms).
(1. Gordon, D.M.: Amer. J. Ophthal. 69:300 [Feb.] 1970. 2. Magnuson, R. H., and Suie, T.: JAMA *199*:427 [Feb. 6] 1967.)

In acute catarrhal conjunctivitis and episcleritis† due to *Staphylococcus aureus* coagulase negative

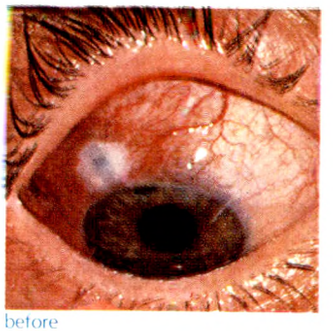


before



after 7 days GARAMYCIN OPHTHALMIC SOLUTION

In infected bleb (post-glaucoma surgery)† due to *Staphylococcus aureus* coagulase negative and *Streptococcus viridans*



before



after 9 days GARAMYCIN OPHTHALMIC SOLUTION

In acute conjunctivitis and dacryocystitis¶ due to pneumococcus



after 7 days GARAMYCIN OPHTHALMIC SOLUTION



after 11 days GARAMYCIN OPHTHALMIC SOLUTION

# New GARAMYCIN® ophthalmic

brand of GENTAMICIN SULFATE SOLUTION/OINTMENT

†Photographs courtesy of D. Gordon, M.D., N. Y. ¶Photographs courtesy of S. Fox, M.D., Baltimore, Md.

# You think it should have flexibility in dosage forms

GARAMYCIN OPHTHALMIC SOLUTION, sterile, isotonic, and buffered to pH of tears, does not blur vision, is well suited to daytime use—supplied in an unbreakable, easy-to-handle dispenser.
GARAMYCIN OPHTHALMIC OINTMENT provides gentle emollient action and keeps medication in contact with tissues for longer periods. It is particularly advantageous for nighttime use or in non-ambulatory patients—supplied in easy-to-use ophthalmic tube.

## Clinical Considerations

**Description:** GARAMYCIN is an antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN Ophthalmic Solution is a sterile aqueous solution buffered to approximately pH 6.7 for use in the eye. Each cc. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN Ophthalmic Ointment contains, in each gram of ointment, gentamicin sulfate (equivalent to 3.0 mg. gentamicin), and methylparaben and propylparaben as preservatives in a bland base of clear petrolatum.

Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

**Indications:** GARAMYCIN Ophthalmic Solution and Ointment are indicated in the topical treatment of infections of the external eye and its adnexa caused by susceptible bacteria. Such infections embrace conjunctivitis, keratitis and keratoconjunctivitis, corneal ulcers, blepharitis and blepharoconjunctivitis, acute meibomianitis, and dacryocystitis.

**Contraindications:** GARAMYCIN Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of the components of these preparations.

**Precautions:** Prolonged use of topical antibiotics may give rise to overgrowth of nonsusceptible organisms such as fungi. Should this occur, or if irritation or hypersensitivity to any component of the drug develops, discontinue use of the preparation and institute appropriate therapy.

**Dosage and Administration:** GARAMYCIN Ophthalmic Solution: One or two drops every four hours. In severe infections, dosage may be increased to as much as two drops once hourly.

GARAMYCIN Ophthalmic Ointment: Apply a small amount to the affected eye two to three times daily.

**How Supplied:** GARAMYCIN Ophthalmic Solution, 5 cc. plastic dropper bottle, sterile, box of 1. GARAMYCIN Ophthalmic Ointment, 1/8 ounce tube, box of 1.

Note: Store away from heat.




Schering

SCHERING CORPORATION, UNION, NEW JERSEY 07083



# We starte at the bottom.

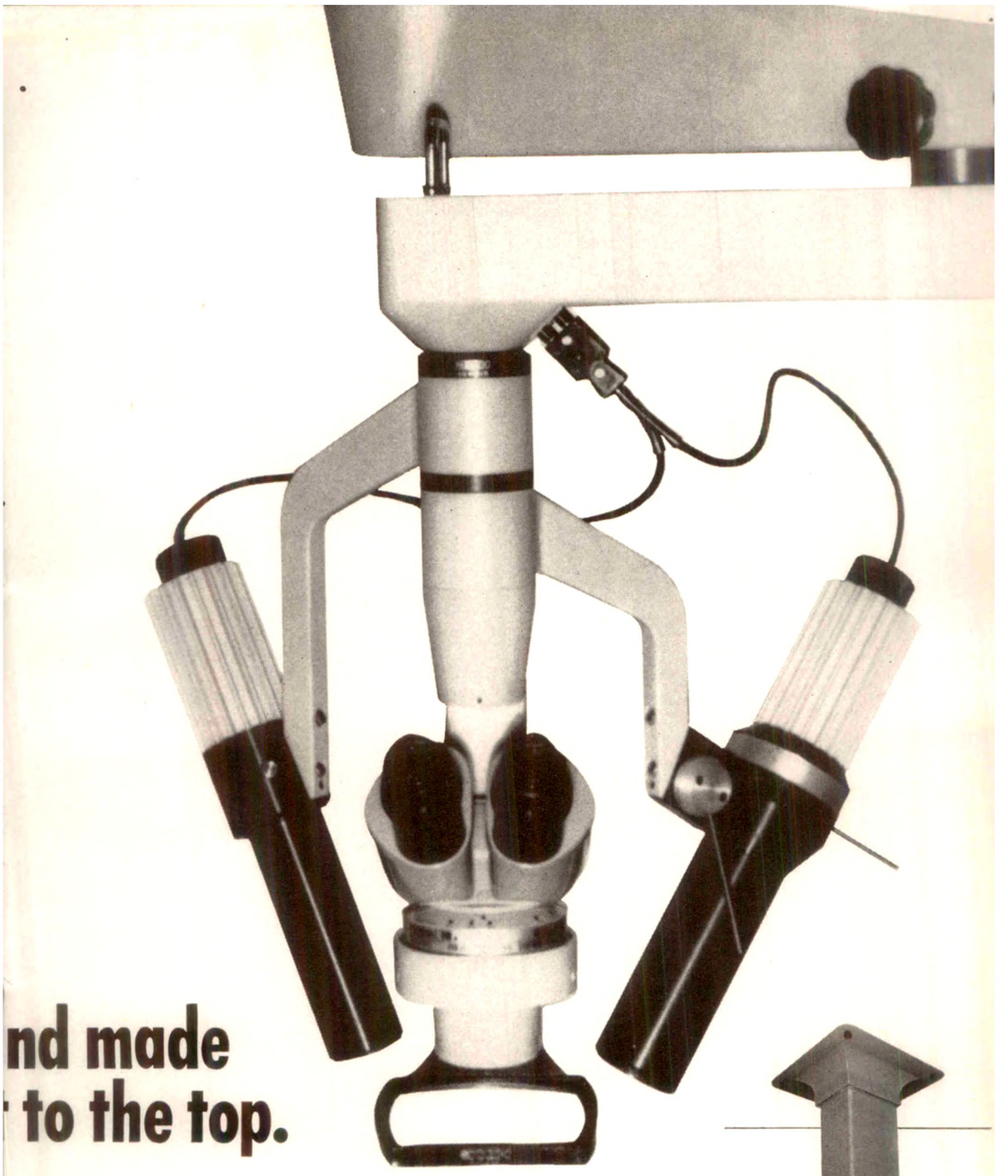
**Troutman Ophthalmic microscopes now co in floor *and* ceiling mounted units.**

A floor and ceiling mounted microscope fit all the required needs of the Ophthal surgeon.

The ceiling mounted microscope has a me ory system that virtually repositions it to exact focal distance. In addition it moves h zontally on a motorized ceiling track. This p mits the operating room to be used for ot than ophthalmic surgery.



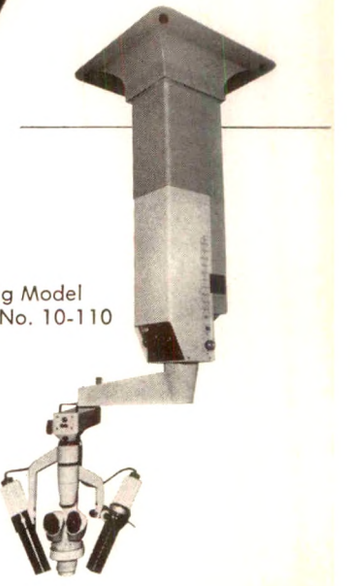
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ECK EDWARD WECK & COMPANY, INC.

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**Caution:** Federal law prohibits dispensing without prescription.

**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902

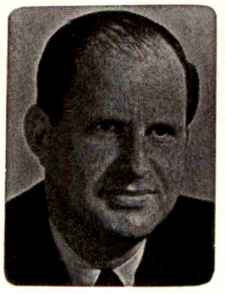
It's a lousy feeling
to wake up in the morning
with your eyelids
stuck together.



No medication residue with Vasocidin.
Nothing to wash away in the morning.
It's an antibacterial, steroid, decongestant combination in true solution.
Works fast because it disperses fast.
Helps relieve nonpurulent blepharitis and conjunctivitis more effectively.
Starts the day right.

# Vasocidin

a clear solution that isn't sticky



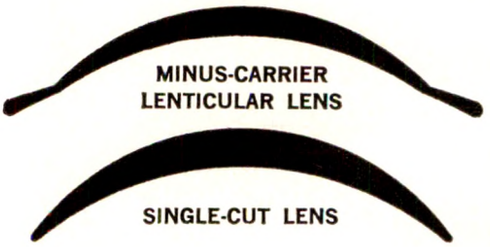
# CONTACT LENSES AND THE APHAKIC PATIENT

## Part 2: Keyhole and Upward-Displaced Pupils

In order to avoid visual disturbances such as flare, ghost images or double vision, it is necessary to fit the aphakic patient so *that the optical portion of the corneal contact lens covers the entire exposed pupil at all times*. With a keyhole or upward-displaced pupil, the lens must usually be positioned somewhat above corneal center to provide this pupillary coverage. Such positioning can often be attained by using a MINUS-CARRIER LENTICULAR LENS which, due to its flat anterior peripheral (carrier) curve, gives the lens periphery *the shape and the performance of a high-minus lens*.

Use of the flat carrier curve increases the upward vector component of the upper lid pull on the contact lens. Thus, with sufficient upper lid cover of the cornea (at least 1.5 mm needed) to grab the lens and pull it up, the lens will usually be held in a position about 1 mm above corneal center. This upward positioning can also be useful for patients with low or very flaccid lower lids, where it is desired to keep the lens from riding down and irritating the lower limbus.

In cases of keyhole pupils or upward-displaced pupils *with little or no coverage by the upper lids*, all aphakic lenses will ride low, and it is often impossible to have optical coverage of the entire pupil with a corneal lens. Sometimes these patients can be fitted with a SINGLE-CUT LENS,



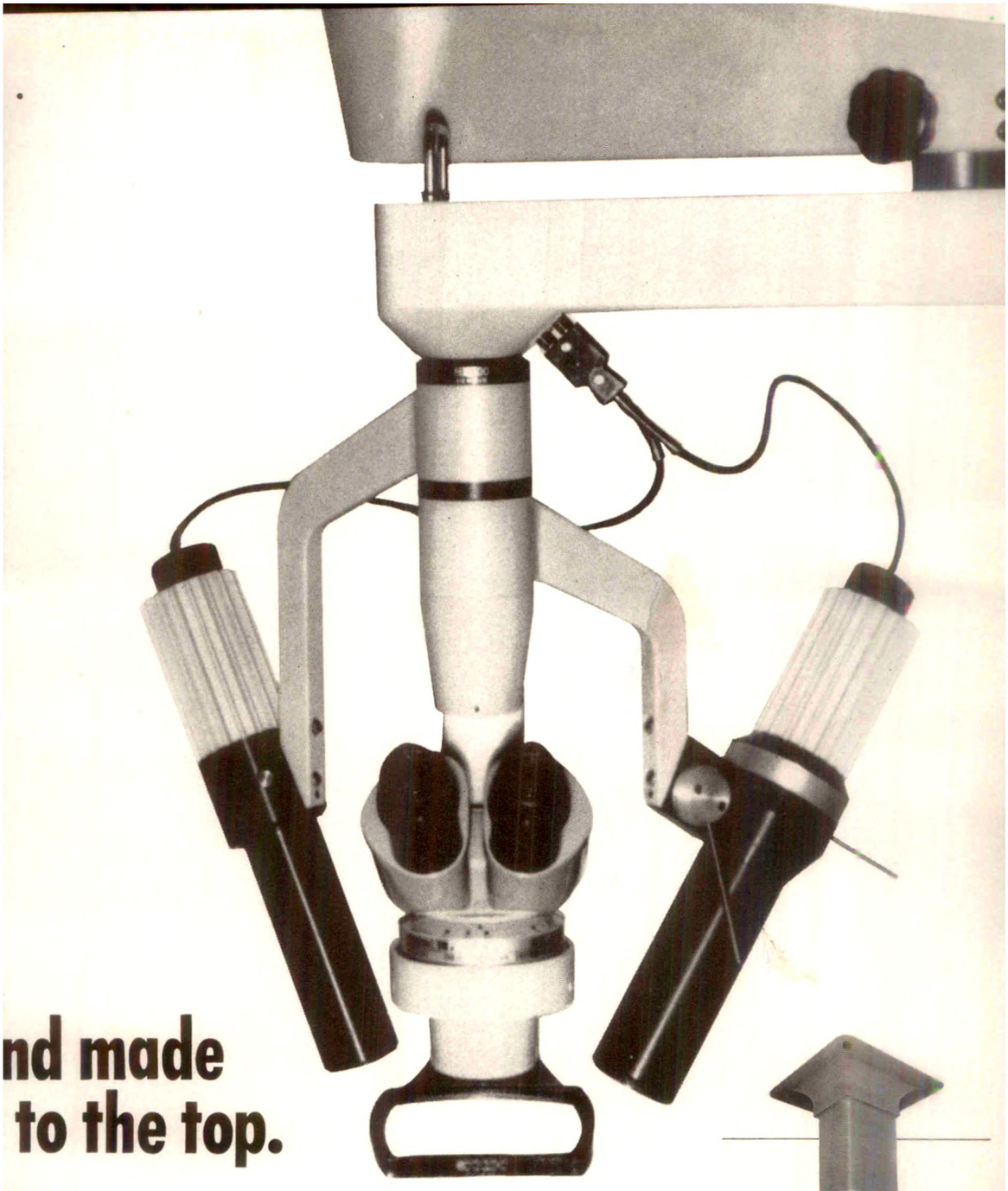

large enough to completely cover the pupil and supported by the lower lid. Such a lens should be made *as small as possible*, because thickness and weight increase very rapidly with size; and it should be made *without any posterior secondary or peripheral curves*, so that the entire lens can be optically functional. For its satisfactory application, a high lower lid is needed, sufficiently tight to support the heavy weight of the lens. Since the lens diameter will be slightly more than the distance from the lower lid to the upper edge of the exposed pupil, it is evident that the higher the lower lid, the smaller (thus thinner and lighter) the lens and the better the chances for successful wear.

STANLEY GORDON, *President*

*(to be continued)*

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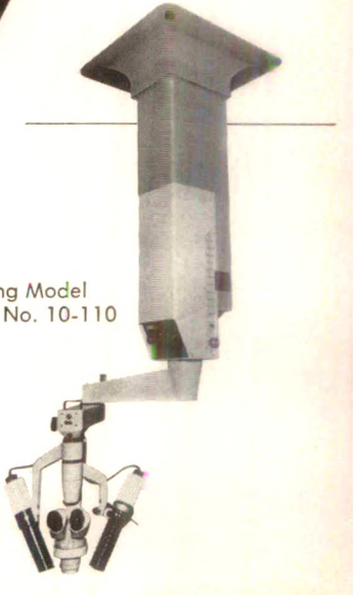
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he floor unit also moves easily on retract-
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during surgery. Both floor and ceiling units
ve foot controlled zoom and focusing, and
illumination with scanning devices.

New Special Options available for both
or and ceiling units:
FIBER OPTIC COAXIAL ILLUMINATION
A 20° TILTING MECHANISM



Ceiling Model
Catalog No. 10-110

*Send for brochure*

ECK **EDWARD WECK & COMPANY, INC.**

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

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Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
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It's a lousy feeling
to wake up in the morning
with your eyelids
stuck together.
No medication residue with Vasocidin.
Nothing to wash away in the morning.
It's an antibacterial, steroid, decon-
gestant combination in true solution.
Works fast because it disperses fast.
Helps relieve nonpurulent blepharitis
and conjunctivitis more effectively.
Starts the day right.
Vasocidin
a clear solution that isn't sticky



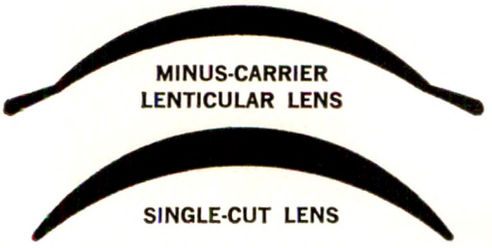
# CONTACT LENSES AND THE APHAKIC PATIENT

## Part 2: Keyhole and Upward-Displaced Pupils

In order to avoid visual disturbances such as flare, ghost images or double vision, it is necessary to fit the aphakic patient *so that the optical portion of the corneal contact lens covers the entire exposed pupil at all times.* With a keyhole or upward-displaced pupil, the lens must usually be positioned somewhat above corneal center to provide this pupillary coverage. Such positioning can often be attained by using a MINUS-CARRIER LENTICULAR LENS which, due to its flat anterior peripheral (carrier) curve, gives the lens periphery *the shape and the performance of a high-minus lens.*

Use of the flat carrier curve increases the upward vector component of the upper lid pull on the contact lens. Thus, with sufficient upper lid cover of the cornea (at least 1.5 mm needed) to grab the lens and pull it up, the lens will usually be held in a position about 1 mm above corneal center. This upward positioning can also be useful for patients with low or very flaccid lower lids, where it is desired to keep the lens from riding down and irritating the lower limbus.

In cases of keyhole pupils or upward-displaced pupils *with little or no coverage by the upper lids,* all aphakic lenses will ride low, and it is often impossible to have optical coverage of the entire pupil with a corneal lens. Sometimes these patients can be fitted with a SINGLE-CUT LENS,




large enough to completely cover the pupil and supported by the lower lid. Such a lens should be made *as small as possible,* because thickness and weight increase very rapidly with size; and it should be made *without any posterior secondary or peripheral curves,* so that the entire lens can be optically functional. For its satisfactory application, a high lower lid is needed, sufficiently tight to support the heavy weight of the lens. Since the lens diameter will be slightly more than the distance from the lower lid to the upper edge of the exposed pupil, it is evident that the higher the lower lid, the smaller (thus thinner and lighter) the lens and the better the chances for successful wear.

STANLEY GORDON, *President*

*(to be continued)*

GORDON CONTACT LENSES INC.
180 ST. PAUL ST. ROCHESTER, N. Y. 14604
Phone 716-232-6878 • Cable CONTACTLENS, Roch., N.Y.
• Metricon • Ultra-Thin Metricon • Astigmacon
• Spiro-Vent • Tangential Periphery • Gordon Bifocal
SUBSIDIARY OF UNION CORP. NYSE SYMBOL—UCO

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Address .....
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## Only Glazcote lets the plastic eyeglass wearer see what he's missing.

Just one dot of Glazcote® on each side of a plastic or hard resin lens fills hair line scratches and helps protect the lenses against future possible scratches. This unique product was developed for the Space Program, for use on spacecraft windows, and to clean, polish and protect astronauts' plastic face shields. And continuous use of optically clear Glazcote helps keep the lenses clean, static free, and polished as well as filling hair line scratches. ALLERGAN Irvine, Calif.; Montreal, Canada

# Recommend Glazcote...just a dot does it.

# NEW DEVELOPMENTS . . .

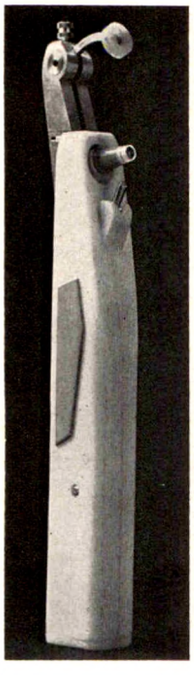


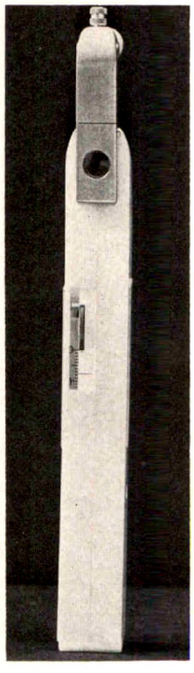
## ORA SERRATA ATTACHMENT TO THE GOLDMANN 3 MIRROR LENS

The periphery of the fundus near the ora serrata and the ciliary body cannot be examined under normal conditions with the 3-mirror lens alone. The ora serrata attachment along with the 3-mirror lens allows the observation of these most peripheral parts in its entire circumference.

The attachment is shaped like the 3-mirror lens. Half a steel-ball is fixed to the scleral part of the attachment which presses on the sclera above the ora serrata so that the fundus at its periphery near the ora serrata can be seen in the gonio mirror of the 3-mirror lens. The ora attachment can be used either with the 3-mirror lens in a locked or moveable position.

## THE PERKINS HAND HELD APPLANATION TONOMETER

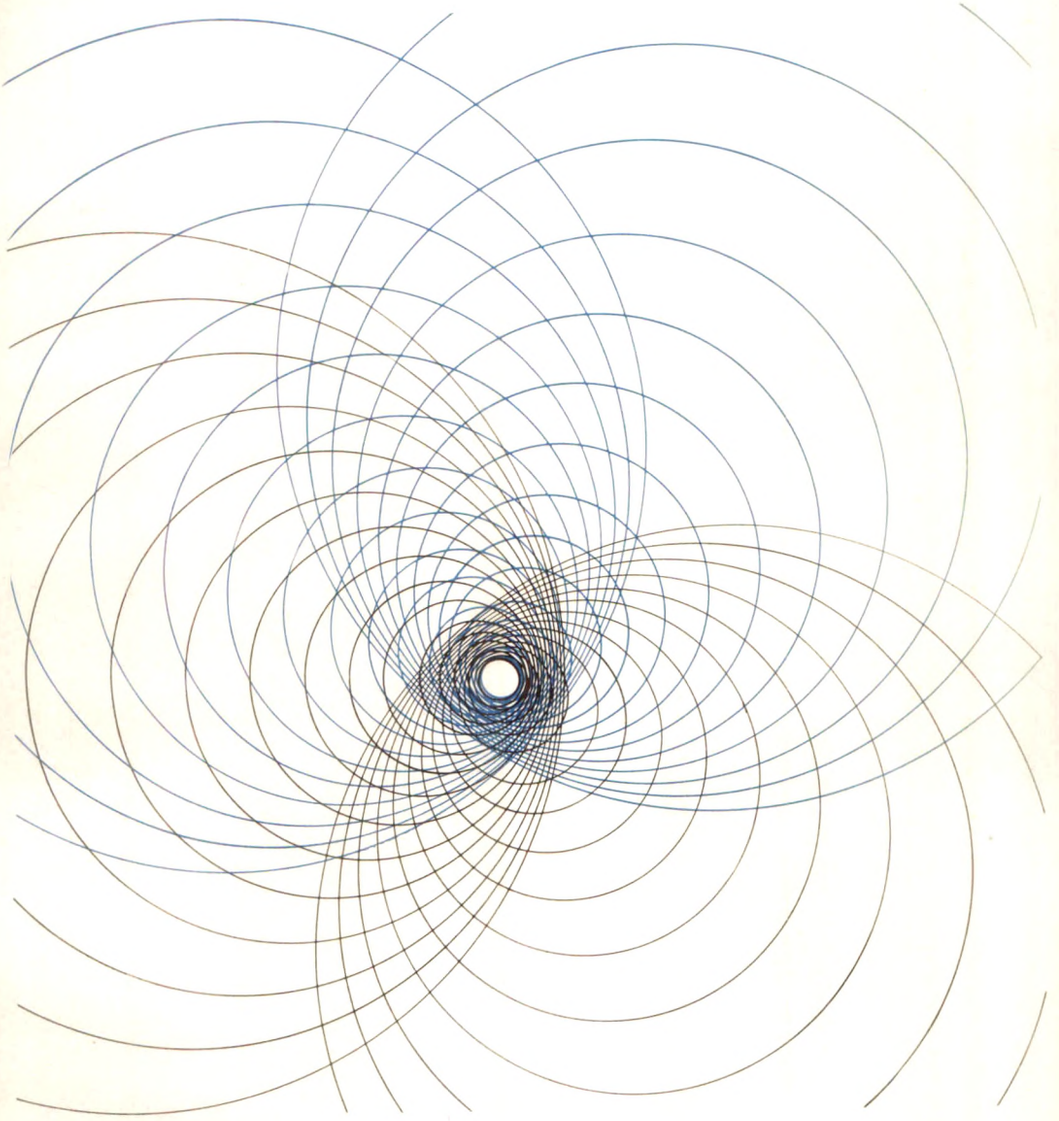




- LIGHT WEIGHT
- GOLDMANN PRISM
- EASY TO USE

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(MADE IN SWITZERLAND)

**ALFRED P. POLL, INC.**
THE HOUSE OF QUALITY OPTICS
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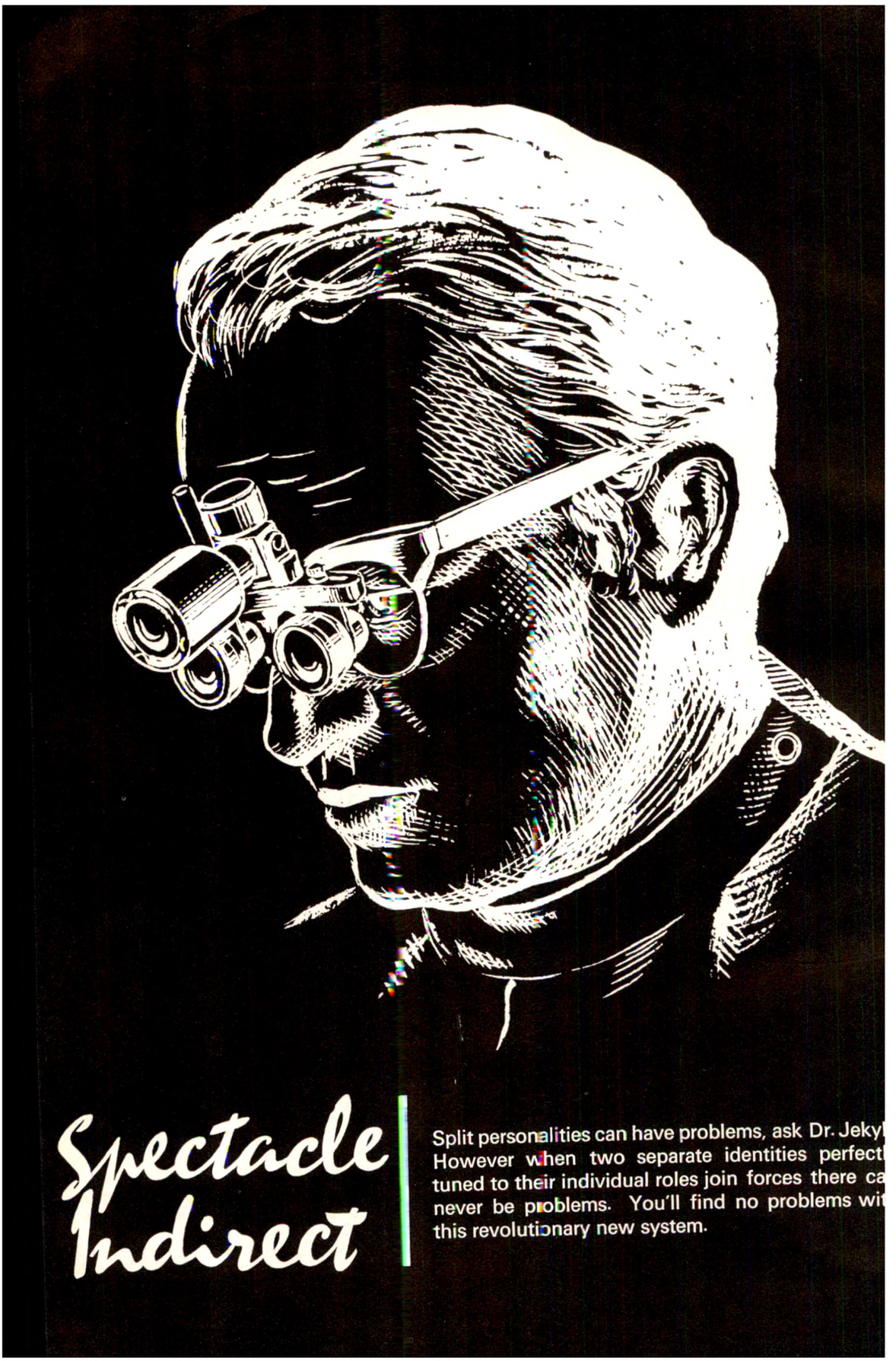


Project 117 unveiled...

...the new **"Stellar"** contact lens.

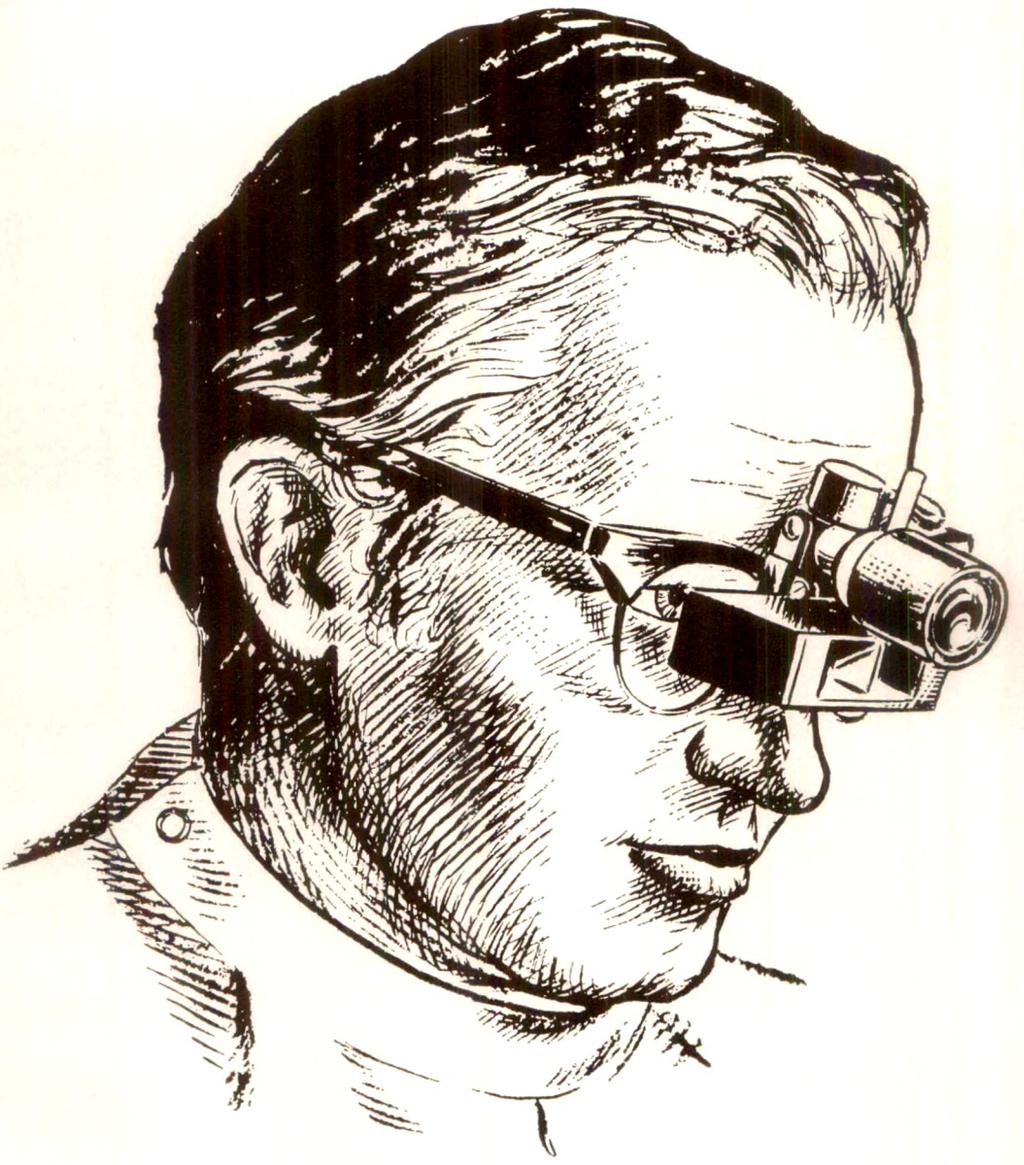
Aspherically engineered and designed for
a natural, more comfortable fit.

**Danker & Wohlk, Inc.**
635 Nassau Road, Uniondale, New York 11553



# Spectacle Indirect

Split personalities can have problems, ask Dr. Jekyl
However when two separate identities perfect
tuned to their individual roles join forces there ca
never be problems. You'll find no problems wit
this revolutionary new system.



The light, bright, stereo-vision Spectacle Indirect Ophthalmoscope (that's fitted so easily) converts in seconds to a spectacle magnifier, with a removable light source and flip-up loupes.

Split personality or marriage of the year? Either way you win with the Spectacle Indirect.

**KEELER**
456 Parkway, Broomall, PA 19008

**Composition:**

**Inflamase**

*Prednisolone Sodium Phosphate .....0.125%
(Equivalent to Prednisolone 0.1%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

**Inflamase Forte**

*Prednisolone Sodium Phosphate 1.0%
(Equivalent to Prednisolone 0.8%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

Prednisolone Sodium Phosphate is a water soluble inorganic ester of prednisolone. It is approximately 2,000 times as soluble in water at 25°C. as is hydrocortisone.

*Licensed under patent #3,134,718.

**Indications:** Inflamase and Inflamase Forte ophthalmic solutions may be used effectively in the following conditions of the anterior segment of the eye: superficial keratitis, including punctate epithelial lesions (Thygeson type), phlyctenular keratoconjunctivitis, and Sjogren's keratoconjunctivitis (with systemic steroids); deep keratitis, including interstitial or parenchymatous keratitis, acne rosacea, sclerosing keratitis; herpes zoster opthalmicus (do not use in herpes simplex); non-purulent conjunctivitis, including vernal, allergic, catarrhal; iridocyclitis; acute iritis; recurrent marginal ulceration, whether endogenous or due to atopic or contact allergies, or microbial allergy; corneal injuries, such as aseptic thermal, radiation, or chemical burns and corneal injuries following surgery or the penetration of foreign bodies; lid allergy; and non-purulent blepheritis, including catarrhal and allergic.

Inflamase and Inflamase Forte ophthalmic solutions have their principal effect on the anterior segment of the eye (cornea and the anterior uvea), with acute disorders responding more favorably than chronic disorders. Inflamase Forte 1% solution is recommended for moderate to severe inflammations particularly when rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

**Dosage:** Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops 2 to 4 times daily.

**Contraindications:** Contraindicated in acute herpes simplex, ocular tuberculosis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal diseases of the eye. Purulent conjunctivitis, purulent blepharitis, and infectious conditions are contraindications to the use of steroids.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

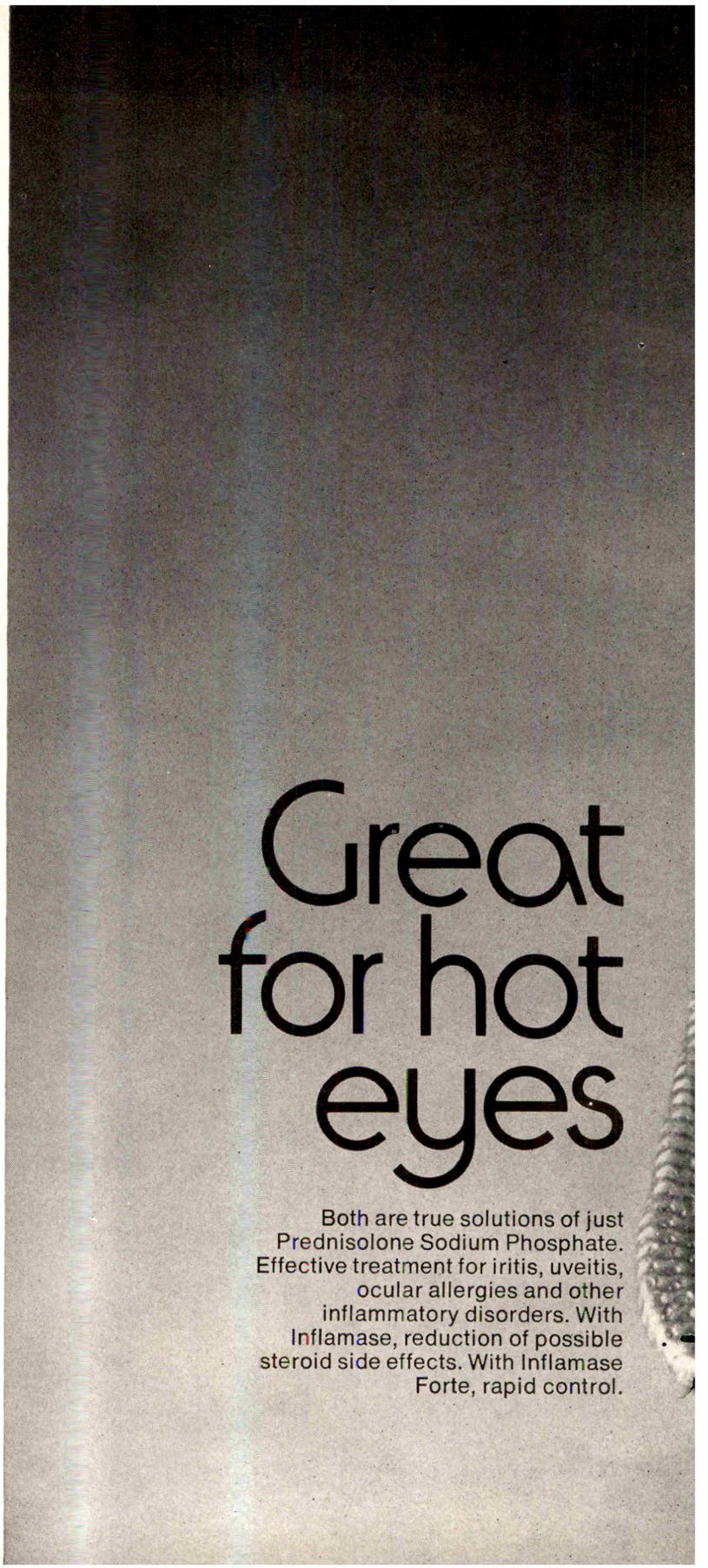
**Warning:** If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.

**How Supplied:** 5 cc plastic squeeze bottle with dropper tip. These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Store in cool place. Protect from light.

**Caution:** Federal law prohibits dispensing without prescription.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902



# Great for hot eyes

Both are true solutions of just Prednisolone Sodium Phosphate. Effective treatment for iritis, uveitis, ocular allergies and other inflammatory disorders. With Inflamase, reduction of possible steroid side effects. With Inflamase Forte, rapid control.



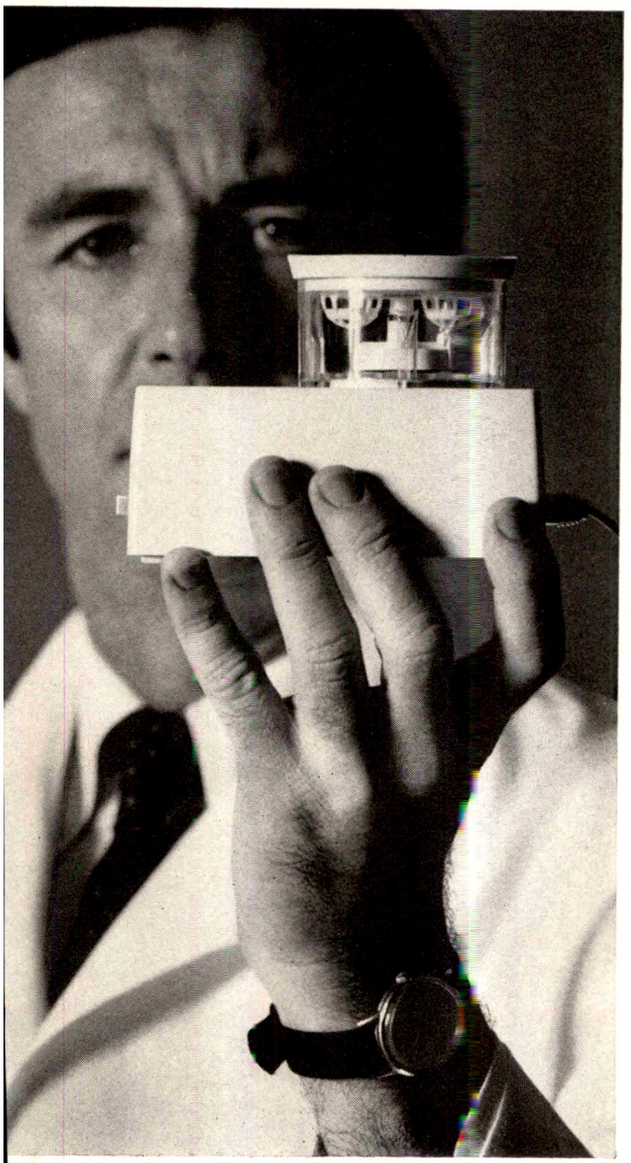

**Inflamase**
for most inflammations.

**Inflamase Forte**
for the tough ones.

# Introducing SWIRL CLEAN™

## electric contact lens cleaner by Contique™

# the professional way to clean contact lenses



Until now, the most common method o cleaning contact lenses has been to rub ther between the fingers. As you know, this syster has three serious drawbacks: 1) it doesn't clea properly; 2) it *can* scratch or warp lenses; 3) may not be sanitary.

### A new, more efficient technique

The new Swirl Clean electric contact len cleaner by Contique approaches the problem i a totally different manner: It combines th cleaning power of a high-speed agitator wit the detergent action of Contique Cleaning Solu tion. The result is thorough but gentle clear ing—with a minimum of handling and les chance of lens loss.

Swirl Clean doesn't stop there. It provide a convenient place to soak and store lenses be tween wearings.

### Perfect for office use

How many times have you wished for jus such an efficient way to clean your patients contacts—when you are delivering a new pai or after making an adjustment?

Swirl Clean fills this long-felt need per fectly. It's compact. Easy to use. And it *look* highly professional. Your patients can se you've gone to the expense of securing the mos advanced cleaning device available to mak sure their lenses are clean and comfortable.

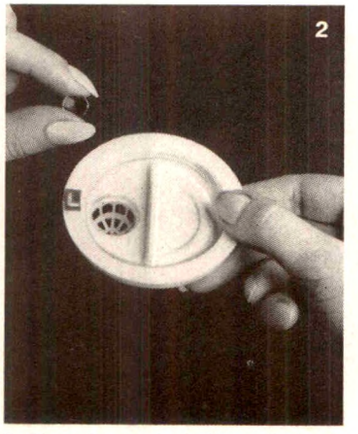
And it takes only a few seconds to clea contacts with the Swirl Clean. Once you get int the habit, you'll wonder how you managed with out it.

### Your patients will want one, too

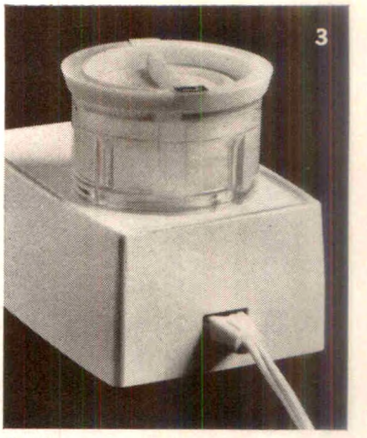
When they see how effortlessly you clea their contacts with the Swirl Clean, your ne contact lens wearers will want one of their ow to use at home. That's why it makes good busi ness sense to stock a few units to sell or recom mend to your patients. They'll never be mor psychologically receptive than at the momen




**1** *Fill cleaning chamber ¾ full with cold water. Add 6-8 drops of Contique Cleaning Solution and place on base.*




**2** *Place lenses in bottom of clearly marked LEFT and RIGHT baskets of lens holder. Close lid. Place lens holder on cleaning chamber.*




**3** *Flip "ON" switch and run Swirl Clean 30-60 seconds. You can see the lenses being swirled clean before your eyes.*

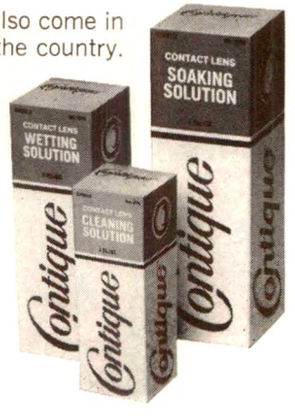
they get their new contacts. It's also a good way of starting them off on a proper lens-care regimen and helping them become satisfied wearers.

### Read what Swirl Clean users say

An O.D. in Knoxville, Tenn. writes: "The compactness of this unit makes its use a pleasure in my office." An M.D. in Bakersfield, Calif. calls Swirl Clean "a very valuable asset to our office." An optician in Long Beach, Calif.: "Excellent method of cleaning lenses after lab adjustment."

Enthusiastic comments have also come in from contact lens wearers all over the country. "My vision is so much better with clean contacts." (Boston, Pa.) "I enjoy its convenience and notice my lenses are more comfortable." (East Point, Ga.) "Cleans lenses 100% better than by hand." (Hyde Park, Mass.) "I wear lenses 16 hours a day and find their comfort greatly increased." (Indianapolis, Ind.)

These comments are on file at Alcon Laboratories and may be examined by anyone interested.



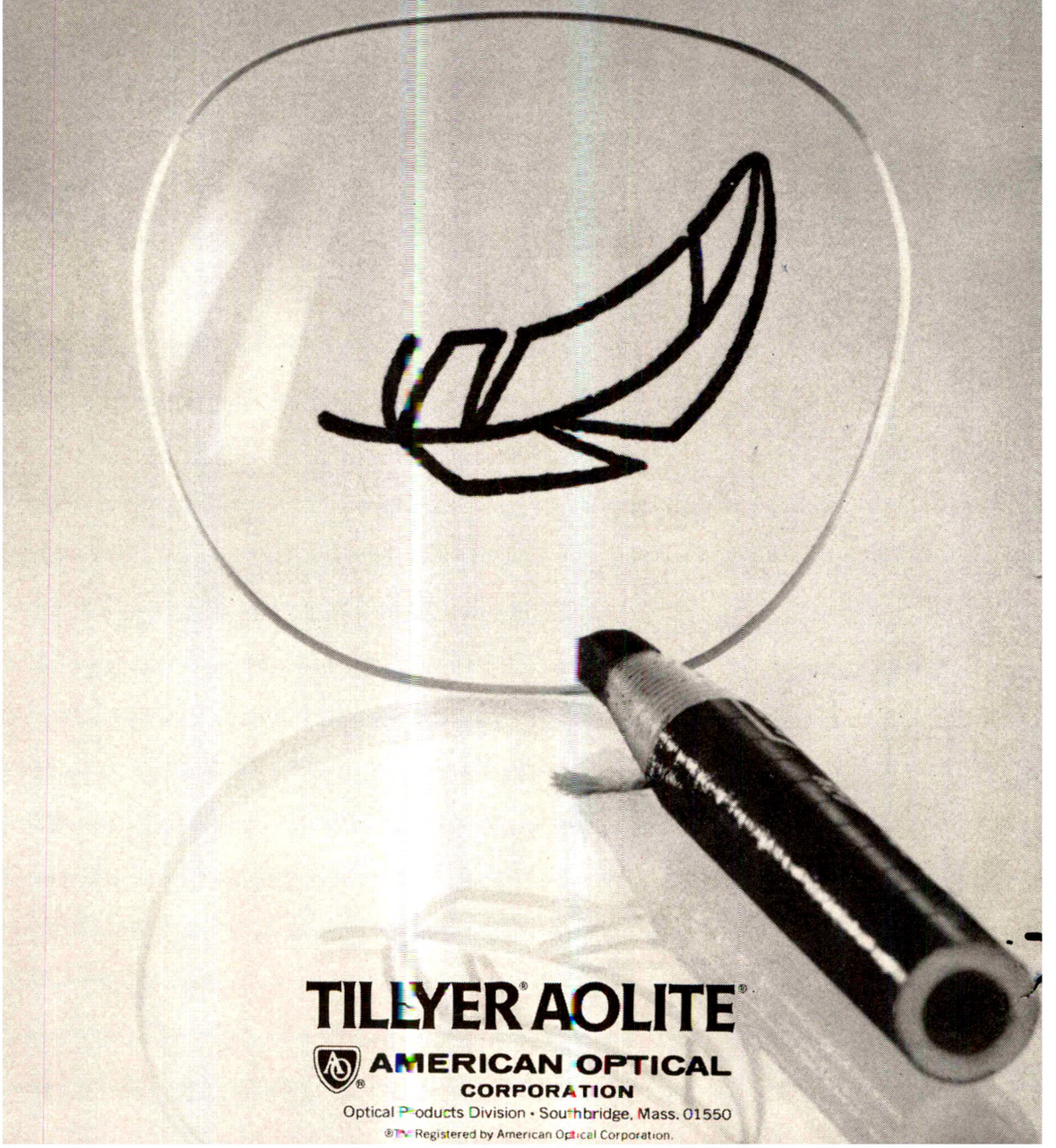

### Complete lens care by Contique

Used with the new Swirl Clean, *Contique Cleaning Solution* dissolves eye-irritating deposits such as mucus, oil and film. Yet it's so gentle you can recommend it with complete confidence. *Contique Soaking Solution* "conditions" lenses by keeping them chemically moist when stored in the special Swirl Clean soaking dish, increasing wettability and wearing comfort. *Contique Wetting Solution* creates a liquid cushion between lens and eyes, makes placement smooth and easy, and can also be used to re-wet lenses during the day.

This family of lens care products from Contique can help your patients become successful, satisfied contact lens wearers. Almost $6 worth of Contique solutions are packed with every Swirl Clean at no additional cost. For more information about the new Swirl Clean and other Contique products, call your optical wholesaler today.

OPTICAL PRODUCTS DIVISION, ALCON LABORATORIES, INC., P.O. BOX 1959, FORT WORTH, TEXAS 76101

# So light your patients hardly know they're wearing it- so strong they're glad they are.



**TILLYER® AOLITE®**

AMERICAN OPTICAL CORPORATION

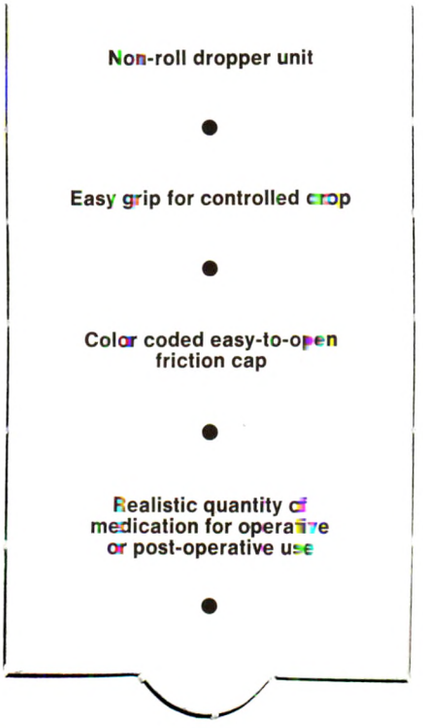
Optical Products Division • Southbridge, Mass. 01550

®TM Registered by American Optical Corporation.

# sterile...
# inside & out



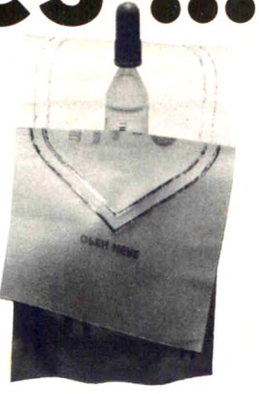

**The Ophthalmic Medication Delivery System for Assured Sterility in the O.R.**


Non-roll dropper unit
Easy grip for controlled drop
Color coded easy-to-open friction cap
Realistic quantity of medication for operative or post-operative use

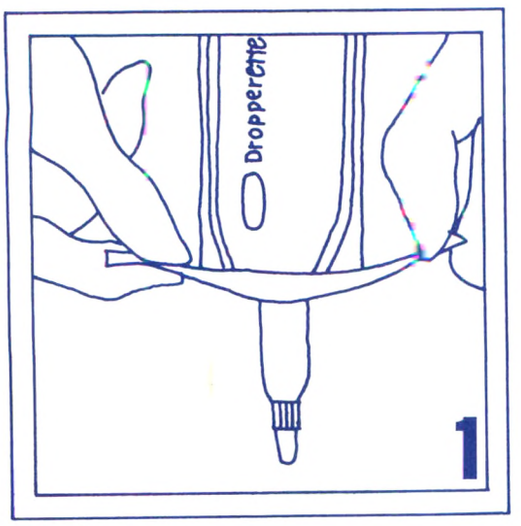
PILOMIOTIN 2%
(Pilocarpine HCl)

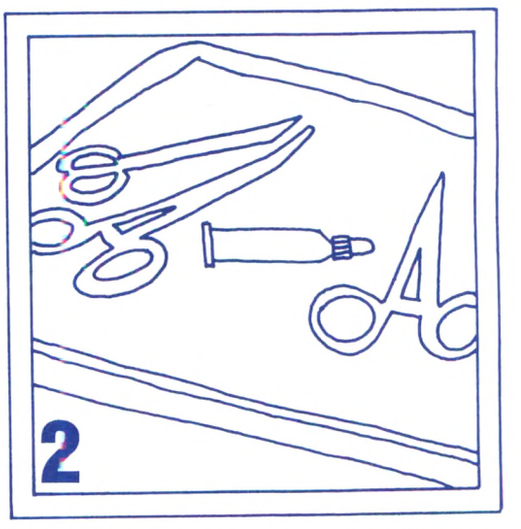
# Dropperettes®...

Sterile Pack



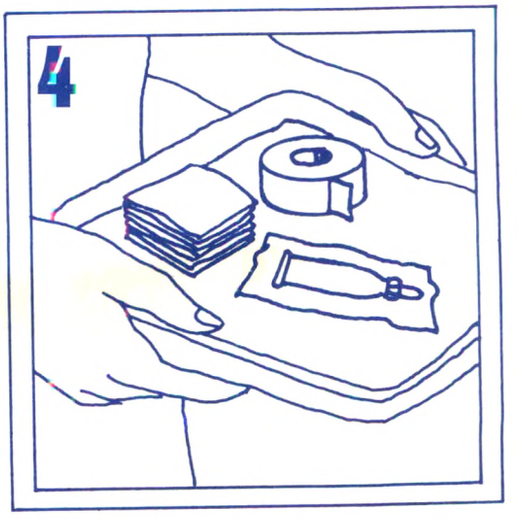
1. Easy-to-handle
2. No compromise in sterility
3. Easy to use during surgery
4. Ideal for post-operative use

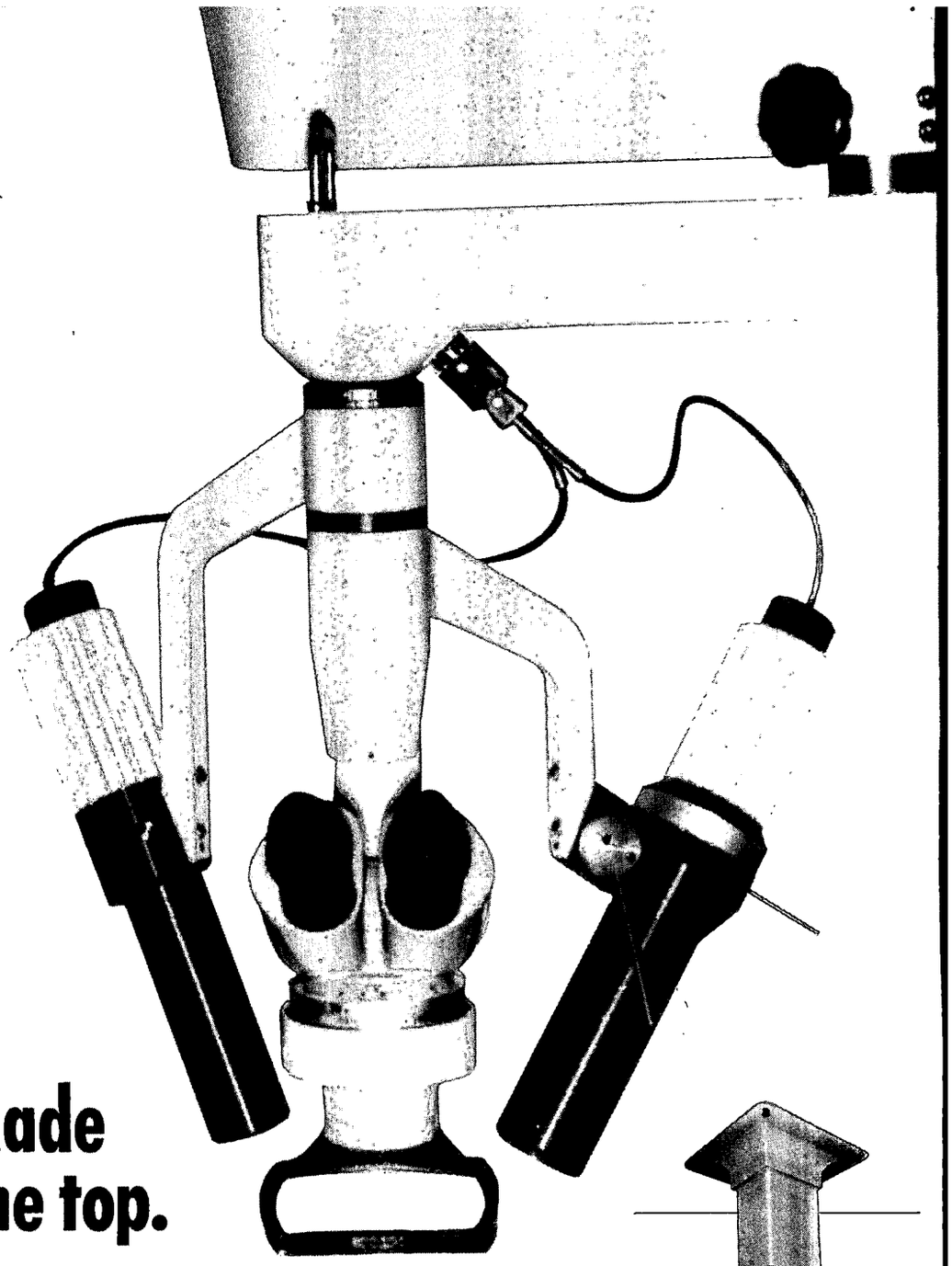



1 When the plastic envelope is peeled apart, a totally sterile DROPPERETTE is ready for delivery to the surgeon or to the instrument tray. Won't roll—flat end design. 2 The outer surface is sterile. Virtually no risk of package edge contamination or contamination of the surgical instrument tray. 3 Extended spout and controlled drop action for ease and accuracy of use. 4 Assures sterile medication delivery at the bedside.



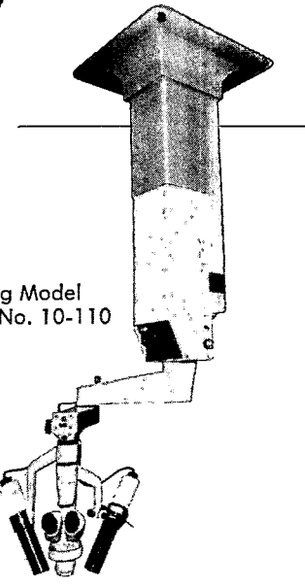





# nd made
# to the top.

The floor unit also moves easily on retractle, conductive casters, yet is absolutely stae during surgery. Both floor and ceiling units ve foot controlled zoom and focusing, and illumination with scanning devices.

New Special Options available for both or and ceiling units:
FIBER OPTIC COAXIAL ILLUMINATION
A 20° TILTING MECHANISM



Ceiling Model
Catalog No. 10-110

*Send for brochure*

**ECK EDWARD WECK & COMPANY, INC.**

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**Caution:** Federal law prohibits dispensing without prescription.

**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

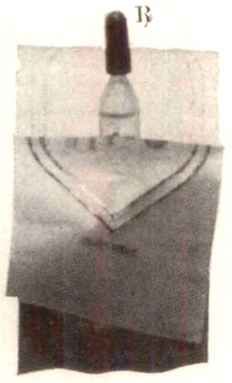
Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

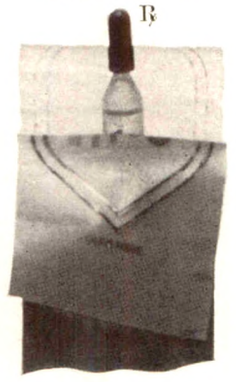
**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick, N.J. 08902

# Frequently Used Ophthalmic Medications . . . In the Most Convenient O.R. Delivery System

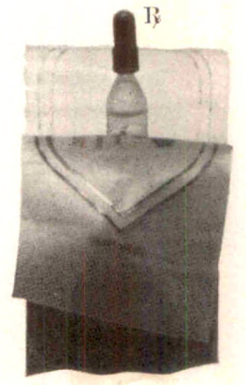
**ARGYROL® S.S. 20% (1 cc.)**



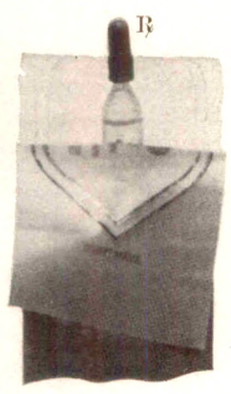
**ATROPISOL® (1 cc.)**
(Atropine Sulfate)
0.5% 1% 2%



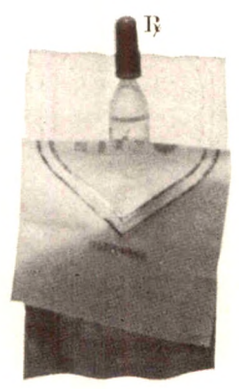
**EPINEPHRINE 1:1000 (1 cc.)**
(as the hydrochloride)



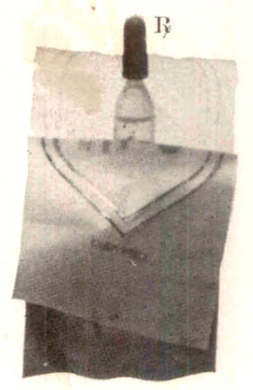
**FLUORESCEIN SODIUM 2% (1 cc.)**



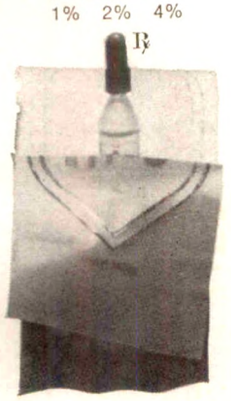
**HOMATROPINE HBr (1 cc.)**
2% 5%



**PHENYLEPHRINE HCl 10% (1 cc.)**



**PILOMIOTIN® (1 cc )**
(Pilocarpine HCl)
1% 2% 4%



**SULFACETAMIDE SODIUM 10% (1 cc.)**

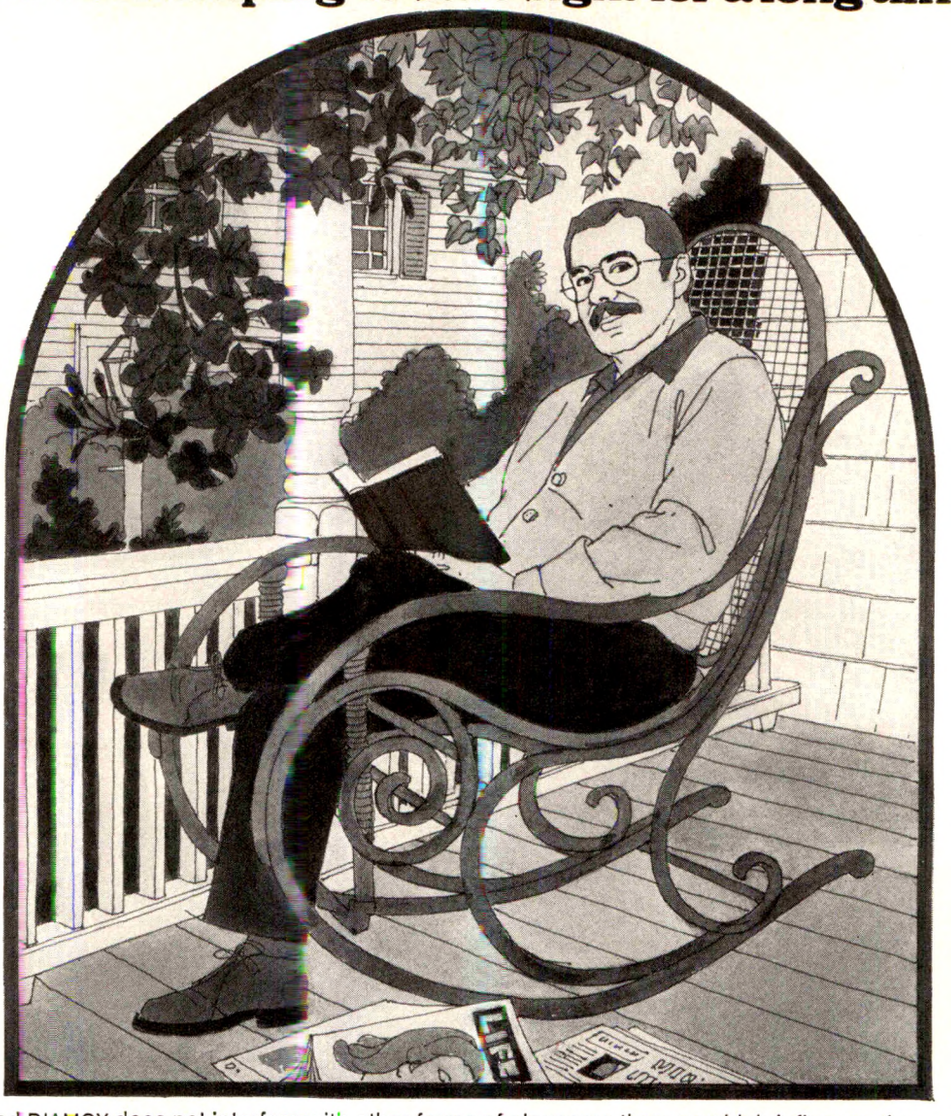


**TETRACAINE HCl 0.5% (1 cc.)**



Cooper COOPER LABORATORIES, INC. WAYNE, NEW JERSEY 07470

# It's been helping to save sight for a long time




And DIAMOX does not interfere with other forms of glaucoma therapy which influence the outflow mechanism. In fact, a complementary effect may be obtained when DIAMOX is used in conjunction with miotics.

Treatment with DIAMOX may retard progress of glaucoma by reducing secretion of aqueous humor and thus intraocular pressure. With DIAMOX SEQUELS, acetazolamide is slowly released, and concentrations peak at 8 to 12 hours. A single dose may provide a therapeutic effect for as long as 18 to 24 hours. It is thus possible to maintain the inhibitory effect on aqueous humor formation with a twice-daily regimen . . . an important consideration for the patient's rest and for minimization of side effects.

**DIAMOX®**
ACETAZOLAMIDE
**SEQUELS®** 500 mg
Sustained Release Capsules

**Contraindications**—Situations in which sodium and/or potassium serum levels are depressed, in kidney and liver disease or dysfunction, suprarenal gland failure and hyperchloremic acidosis. Long-term administration is contraindicated in chronic noncongestive angle closure glaucoma.

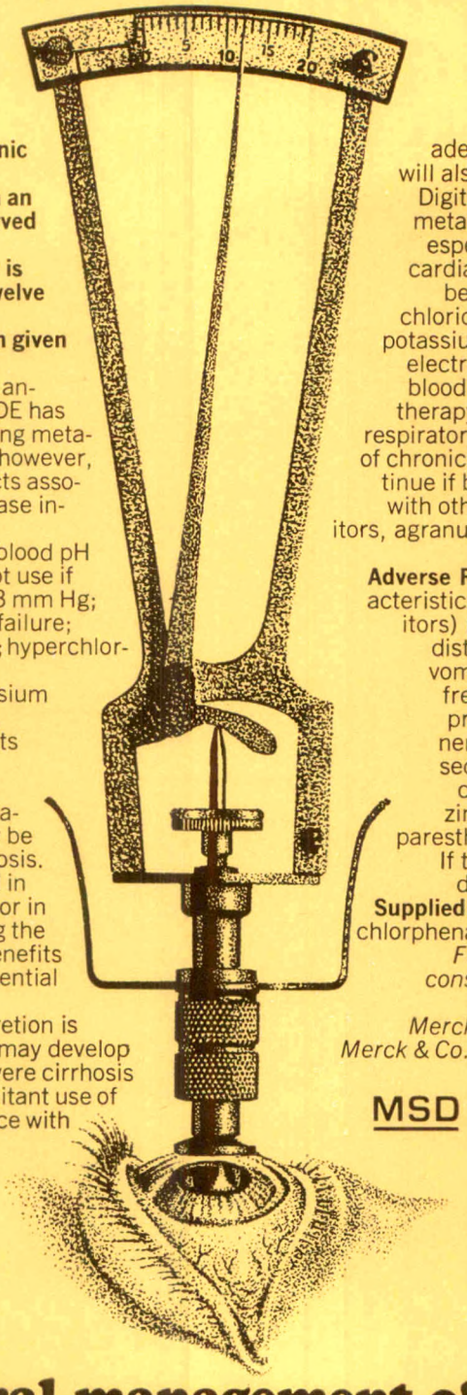
**Warning**—Although teratogenic and embryocidal effects demonstrated in mice at more than ten times the equivalent therapeutic doses have not been evidenced in humans, DIAMOX Acetazolamide should not be used in pregnancy, especially during the first trimester, unless the expected benefits outweigh these potential adverse effects.

**Precautions**—Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Reactions common to sulfonamides may occu fever, rash, crystalluria, renal calculus, bone marrow depression, thro bocytopenic purpura, hemolytic anemia, leukopenia, pancytopeni agranulocytosis. If such occur, discontinue drug and institute appropria therapy.

**Side Effects**—During short-term therapy: paresthesias, loss of appeti polyuria, drowsiness, confusion. In long-term therapy an acidotic sta may supervene. Transient myopia has been reported. Other occasional r actions: urticaria, melena, hematuria, glycosuria, hepatic insufficienc flaccid paralysis, convulsions. 354

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965

# the measure of success...



- **orally effective, potent carbonic anhydrase inhibitor**
- **onset of action usually within an hour; maximal effect is observed in two to four hours**
- **lowered intraocular pressure is often maintained for six to twelve hours**
- **usually most successful when given in conjunction with miotics**

Compared to other carbonic anhydrase inhibitors, DARANIDE has a lesser propensity for causing metabolic acidosis. Please note, however, that this and other side effects associated with carbonic anhydrase inhibitors may occur.

**Contraindications:** To avoid blood pH decreases below 7.20, do not use if arterial $pCO_2$ greater than 63 mm Hg; hepatic insufficiency; renal failure; adrenocortical insufficiency; hyperchloremic acidosis; conditions in which sodium and/or potassium serum levels are depressed. Should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased to the point of narcosis.

**Warning:** Should not be used in women of child-bearing age or in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh potential adverse effects.

**Precautions:** Potassium excretion is increased and hypokalemia may develop with brisk diuresis, when severe cirrhosis is present, or during concomitant use of steroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Hypokalemia may be treated by use of potassium chloride or giving foods with a high potassium content. A close check on electrolyte balance, blood pH, and blood gases should be kept during therapy. Use with caution in severe respiratory acidosis or in the presence of chronic pulmonary infection; discontinue if blood pH falls below 7.20. As with other carbonic anhydrase inhibitors, agranulocytosis, thrombocytopenia, or renal calculi are possible.

**Adverse Reactions:** Side effects (characteristic of carbonic anhydrase inhibitors) may include gastrointestinal disturbances (anorexia, nausea, vomiting), constipation, urinary frequency, mild skin eruptions, pruritus, headache, weakness, nervousness, globus hystericus, sedation, lassitude, depression, confusion, disorientation, dizziness, ataxia, tremor, tinnitus, paresthesias of hands, feet, tongue. If they occur, reduce dosage or discontinue drug temporarily.

**Supplied:** Tablets containing 50 mg dichlorphenamide each, in bottles of 100.

*For more detailed information, consult your MSD representative or see the Direction Circular.*

*Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

MSD MERCK SHARP & DOHME

## ...in the oral management of glaucoma

# DARANIDE®



## [DICHLORPHENAMIDE | MSD]

TABLETS, 50 mg


stable at
room temperature
for three years
needs no
refrigeration
needs no
reconstitution
Rx
needs no
eyedropper

Modern materials and design techniques have made this camera more versatile and easier to use than older types, and lowered the cost as well.

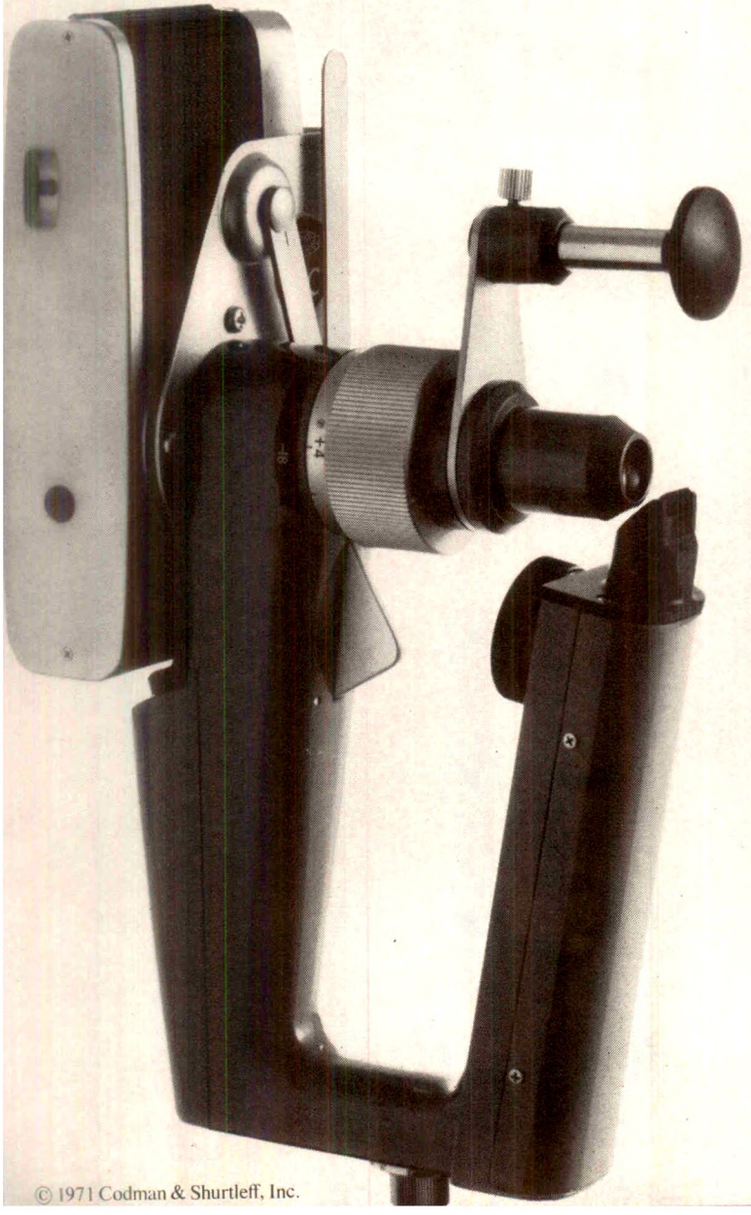
The Olympus Fundus Camera from Mentor is light, compact, balanced – ideal for office diagnosis and records. No additional apparatus is required for very sharp, evenly illuminated photographs – regardless of patient or camera movement.



Trigger, lens selection, and fine focusing are controlled by one hand while you view the area of interest through a bright, clear viewing system. Diopter settings range from +16 to −22 (making external photographs possible) including ±4 of fine focus. Newly developed objective optics completely eliminate spurious light reflections and produce excellent color records – 40 on a standard 20-exposure roll.

There is nothing like the Olympus Fundus Camera from Mentor and there is nothing like its price: $985 complete. Write for full information. Mentor Division, Codman & Shurtleff, Inc., Randolph, Mass. 02368.

Codman Mentor
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Fundus photography has come a long way.

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## in open-angle glaucoma

# HUMORSOL®

## (DEMECARIUM BROMIDE | MSD)

OPHTHALMIC SOLUTION, 0.125% and 0.25%

## the cholinesterase inhibitor that needs no pampering



IN OCUMETER® OPHTHALMIC DISPENSER

**FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY**

**Contraindications:** Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

**Warnings:** Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

*Use in Pregnancy:* Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

**Precautions:** Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

**Adverse Reactions:** Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. Similar therapy is indicated for overdosage.

Lens opacities have been reported, and routine slit-lamp examinations should accompany prolonged use. Paradoxical increase in intraocular pressure may occur and be alleviated by a mydriatic.

**Dosage and Administration:** Initial titration and dosage adjustments must be individualized to obtain maximal therapeutic effect. Patient must be observed closely during initial period. If response is not adequate within first 24 hours, consider other measures. Keep frequency of use to a minimum in all patients, but especially in children.

Since technic is crucial to proper and safe administration, consult Direction Circular for full details.

**Supplied:** In 5-cc OCUMETER® Ophthalmic Dispenser containing 0.125 or 0.25 percent solution and sodium chloride; benzalkonium chloride 1:5000 added as preservative.

*For more detailed information, consult your MSD representative or see the Direction Circular. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

MSD
MERCK SHARP & DOHME

# THE 3RD DIMENSION IN DIAGNOSIS...MOSBY STEREOSCOPIC ATLASES

**MANAGEMENT OF DIABETIC RETINOPATHY—A Stereoscopic Presentation,** *New: by Edward Okun, M.D.; Glen Paul Johnston, M.D.; and Isaac Boniuk, M.D.* For the first time in book form full color stereophotographs demonstrate each specific diabetic lesion as it appears before treatment, immediately after treatment, as well as months and even years later. Precise descriptions bring you current treatment data on xenon and argon photocoagulation, pituitary ablation, and scleral buckling in retinal detachment. Emphasizing case selection, the authors suggest which types of eyes should be treated and what therapy is most effective. Their corresponding statistical analysis profiles long-term results. *October, 1971. Approx. 208 pages, 8½″ × 11″, 314 illustrations, 112 stereoscopic views in full color on 16 View-Master (R) reels and a View-Master (R) compact viewer. About $50.75.*

**ATLAS OF EXTERNAL DISEASES OF THE EYE, Vol. III, Cornea and Sclera,** *New: By David D. Donaldson, M.D.* Increase your ability to recognize conditions affecting the cornea and sclera with the newest stereoscopic atlas in this dynamic series! Concise discussions and actual case histories join with full-color stereoscopic views and complementary black and white illustrations to present new insight into congenital syndromes, corneal signs of systemic disease, bacterial infections and iatrogenic disease. Not only does this atlas emphasize diagnosis, but its stereoscopic views provide a superior way of examining corneal diseases, since most two-dimensional photos of such conditions frequently superimpose corneal defects onto the iris pattern. *June, 1971. 466 pages plus FM I-XIV, 8½″ × 11″, 252 illustrations, 112 stereoscopic views in full color on 16 View-Master (R) reels and a View-Master (R) compact viewer. Price, $69.50.*

**STEREOSCOPIC ATLAS OF CLINICAL OPHTHALMOLOGY OF DOMESTIC ANIMALS,** *New: By H. E. Jensen, D.V.M.* Another first of its kind, this unique atlas stereoscopically demonstrates most generally encountered pathologic conditions in animal ophthalmology. It combines full-color stereoscopic views with concise descriptions and pertinent illustrations to fully detail each of these disorders. You'll find these comprehensive studies to be valuable aids for comparative ophthalmology research and clinical studies. *May, 1971. 201 pages plus FM I-XIV, 8½″ × 11″, 134 illustrations, 112 stereoscopic views in full color on 16 View-Master (R) reels, and a View-Master (R) compact viewer. Price, $49.50.*

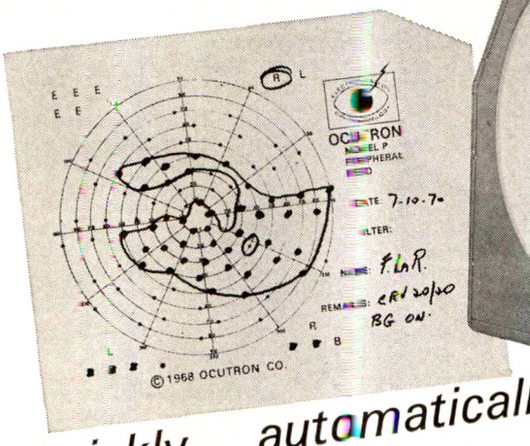
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# *Now* OCUTRON®

## *offers you visual fields*

. . . whenever you want
. . . as often as you want
without your being there






## *quickly . . . automatically!*

U.S. Patent Nos. 3,288,546
and 3,421,498

The Ocutron® Visual Field Tester, developed by a leading ophthalmologist, is a highly precise electronic instrument that automatically examines the visual field and records it permanently on the standard chart that you are accustomed to using and interpreting.

Without the presence of doctor or nurse, the patient tests himself by push-button response to stimuli of standard light targets as they appear within the white hemisphere. This response is electrically registered on the chart.

Difficult and time-consuming fields like the above glaucoma field are as easily and quickly tested as a simple normal field.

Background may be lighted or not, as desired, for light or dark adapted fields. Built-in check on patient fixation and patient reliability.

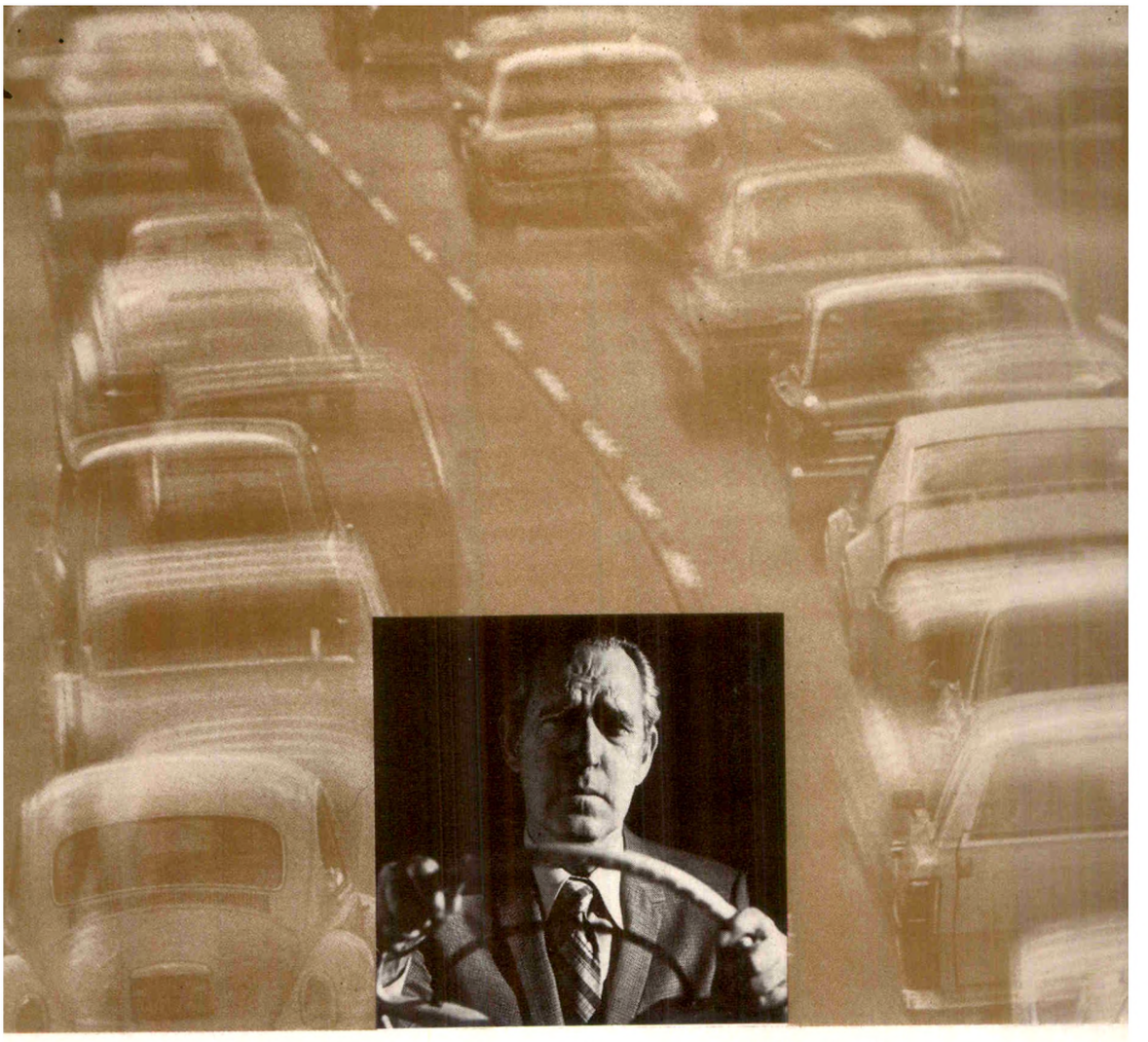
Particularly suitable for high volume performance. Simple enough for screening. Accurate enough for definitive, repeatable field study.

For further information write for new literature
or contact your ophthalmic distributor.

ELECTRONICS FOR OPHTHALMOLOGY

## OCUTRON COMPANY

22500 South Woodland Road
Cleveland, Ohio 44122



In an environment of repeated irritation...

## one drop of Albalon™ provides over 190 minutes of the most potent decongestant activity.

In a recent double blind study,* the superior decongestant activity of Albalon™ Liquifilm® was clearly demonstrated. Compared to three of the most familiar vasoconstrictors, just one drop of Albalon™ provided both immediate, effective eye-whitening, and 190 minutes of the most potent protection against repeated ocular insult.

Additionally, Albalon™ comes in the Liquifilm® vehicle to soothe, lubricate and comfort itchy, smarting, red eyes.

*from an independent study conducted on a controlled population; data on file, Allergan Research Department.

**Contains:** naphazoline HCl, 0.1%; Liquifilm® (polyvinyl alcohol), 1.4%; with benzalkonium chloride, disodium edetate, citric acid, sodium citrate, sodium chloride, sodium hydroxide and purified water. **Indications:** For use as a topical ocular vasoconstrictor. **Contraindications:** Hypersensitivity to the components of this preparation. **Precautions:** This preparation should be used only with caution in the presence of hypertension, cardiac irregularities, hyperglycemia (diabetes), hyperthyroidism. **Adverse Reactions:** Pupillary dilatation, increase in intraocular pressure, systemic effects due to absorption (i.e. hypertension, cardiac irregularities, hyperglycemia). **Warnings:** Should not be used in patients with narrow angle glaucoma. If irritation persists, or increases, discontinue use. **Dosage and Administration:** One to two drops instilled in each eye every three to four hours or less frequently, as required to relieve symptoms.

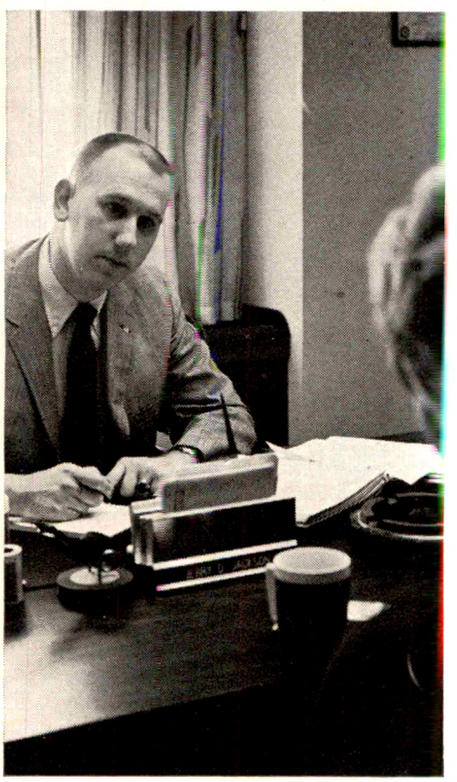
Rx **Albalon**™ LIQUIFILM® Ophthalmic Solution
(naphazoline HCl)

ALLERGAN Irvine, California / Montreal, Canada

# Who needs contact lens insurance?

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# and ...
# your patients do!



It's amazing how some contact lens specialists think of contact lens insurance this way. Maybe it's not as amazing as it is appalling.

RLI's contact lens insurance program has a proven record for reducing a patient's natural apprehension about loss. And this can make your job easier.

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RLI—the practical solution to the lost and damaged lens problem.

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*"The company that cares about continuing eye care"*

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***We now insure ALL soft contact lenses!***

Specific for
Herpes Simplex Keratitis

**STOXIL®**
**brand of IDOXURIDINE**

the only brand of IDU
available in two forms:
Solution—Ointment

Both now available in Canada




# The choice is yours

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

**Indications:** Only in the treatment of herpes simplex keratitis.

**Description: 'Stoxil' Ophthalmic Solution** contains idoxuridine (5-iodo-2'-deoxyuridine) **0.1% (1 mg./ml.)** in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. **'Stoxil' Ophthalmic Ointment** contains idoxuridin **0.5% (5 mg./gram)** in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

**Contraindications:** Contraindicated in patients with known or suspected hypersensitivity to any of its components.

**Precautions:** Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

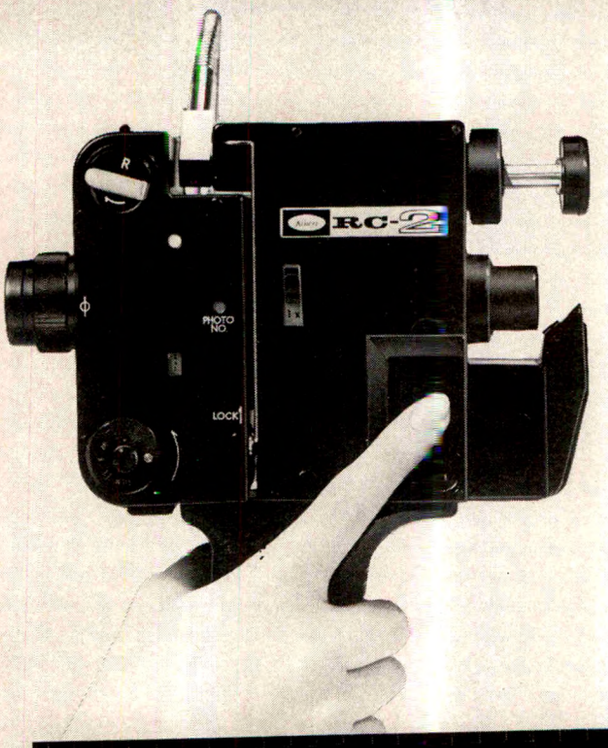
'Stoxil' Ophthalmic Solution should not be mixed with other medications.

**Adverse Reactions:** Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

**How Supplied:** 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

**Stability:** The Solution should be stored in refrigerator until dispensed. The Ointment does not require refrigeration.

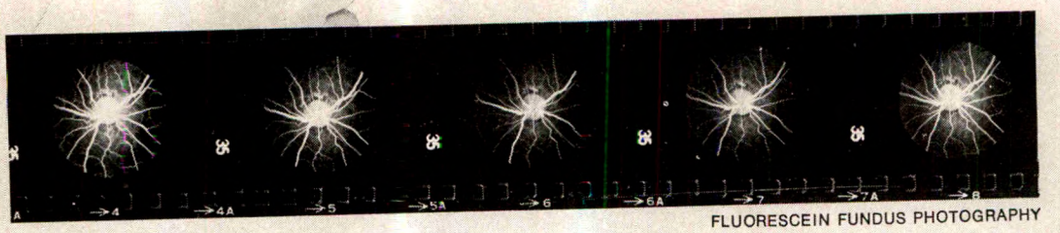
SK&F Smith Kline & French Laboratories




# Kowa RC-2

## fundus camera

*The simple approach to fundus and fluorescein photography.*




FLUORESCEIN FUNDUS PHOTOGRAPHY

To be fully meaningful to the medical profession, all instrumentation must function as an extension of the user's eyes, hands, and mind. The Kowa RC-2 fundus camera fully embodies this principle.

- *Fundus and External Photography* The basic RC-2 incorporates every conceivable advance in optics, mechanics, and electronics. Standard are built-in flash, 2X magnifying lens automatic frame numbering for patient coding, and more. It will produce impeccable 35mm results even for inexperienced users.

- *Fluorescein Photography* By simply adding an auto-wind back, filters, and a quick-cycling power unit, the RC-2 becomes a flawless fluorescein photographic instrument.

- *Polaroid® Photography* An attachment gives you 60-second fundus photographs.

To see why the *total systems approach* has made Kowa's RC-2 the standard by which all others are measured, contact the representative in your area.

**Kowa Company, Ltd.**
**No. 3, 3-CHOME, NIHONBASHI-HONCHO, CHUO-KU, TOKYO 103, JAPAN**

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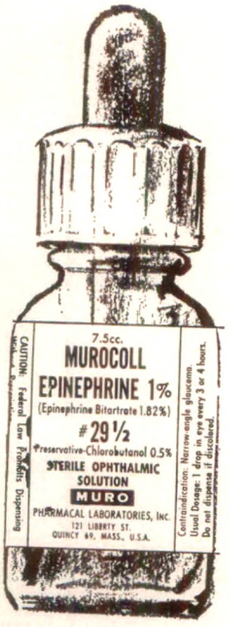
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IMPERIAL OPTICAL COMPANY, LTD.
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# MUROCOLL EPINEPHRINE 1%

**As (L-Epinephrine Bitartrate 1.82%)** **PRODUCT #29½**




- Effective in maintaining lowered intraocular pressure in certain cases of open angle glaucoma by reducing the rate of aqueous formation.
- Improves the facility of outflow after prolonged therapy in more than 50% of eyes with open angle glaucoma.*
- Aids in breaking posterior synechiae in uveitis.

Murocoll Epinephrine 1% (as Bitartrate 1.82%) with Chlorobutanol 0.5% as a preservative and bacteriostatic agent is also available as Murocoll Epinephrine 2% (as Bitartrate 3.64%), Product #29.

Both solutions also have Sodium Bisulfite as preservative; Sodium Chloride and distilled water as inactive ingredients.

Above solutions are contraindicated in narrow angle glaucoma. Use with caution in presence of hypertension.

Available: 7.5 cc. glass bottle with plastic dropper. ℞ only

**Patient does not have to refrigerate above solutions.**

Complete Ophthalmological Formulary Available On Request

Originators of Stabilized Epinephrine Collyria

*BECKER ET AL. TR. SEC. A.M.A. 188, 1961

Muro preparations are available to all pharmacies and hospitals through their drug wholesaler, or may be obtained directly from our laboratories by indicating their usual source of supply.

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# Jet or Drop

***DACRIOSE gives you complete control of ocular irrigation. You can provide a gentle but thoroughly cleansing "jet-like" action . . . or you can use it drop-by-drop.***

This modern irrigating solution, in the unique *Jet-Stream* dispenser, is ready-to-use and self-sterilizing.

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☐ *In the office:* after tonometry and gonioscopy — to wash away fluorescein — to wash out secretions and discharges.

☐ *In the emergency room:* for quick, safe removal of foreign bodies.

☐ *In the operating room:* for sterile and convenient irrigation of the eye pre- and post-operatively.

☐ *At the bedside:* to clean and irrigate eyes — to save staff time.

**Formula:** A sterile, stable, buffered isotonic solution of boric acid, sodium carbonate, potassium chloride. Preserved with benzalkonium chloride, 0.01%; with 0.01% disodium ethylenediamine tetraacetate.

**Warning:** Do not dilute or reuse the solution. Do not touch dropper tip to eye or any surface as this may contaminate solution.

**Supply:** 0.95 fl. oz. and 4 fl. oz. plastic Irrigator bottles.

## DACRIOSE®

you control the flow — sterile and self-sterilizing — isotonic




Cooper

**COOPER LABORATORIES, INC.**

**Tillyer Topics**



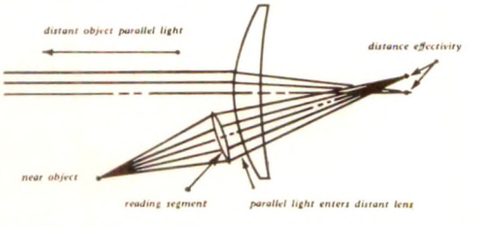
E. WILLIAM TILLYER

# LENSOMETER® lens measuring instrument

The Lensometer is a meter or instrument designed to measure the power of a lens when light enters the lens in parallel rays. It gives the power in dioptric values. The basic optical design of Lensometer instruments is almost fifty years old. But the function and limitations are still often misunderstood.

The Lensometer instrument is very accurate in checking the power of a single-vision lens or the distance portion of a multi-focal lens. However, when checking the power of a bifocal addition, it is important to understand the limitations of the Lensometer instrument.

When you refract, you first determine the patient's requirements for comfortable distance vision. You then add to his correction the amount of plus power required for comfortable near vision. This requirement is for vision at 13″ to 16″—*and the rays of light as they come from this near image to the eye are divergent.*




Your prescription, as it is written, indicates that you have given your patient a certain amount of power for distance. And then added a plus lens for near vision. When the prescription has been made up, it should be checked on the Lensometer instrument to make sure the Rx is what you ordered for your patient.

Therefore, you check the Rx with the convex side of the lens toward you. The Lensometer instrument will give a true and accurate reading for the distance portion. But if you check the power through the segment—without reversing the lens in the instrument—the difference between the distance power and the power through the segment will not always equal the power you prescribed as an addition.

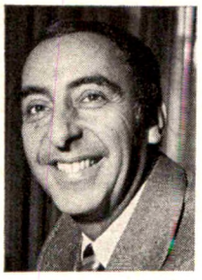
This is because the segment of the lens is being measured for use at infinity. Whereas you prescribed the addition for use at near, with rays divergent rather than parallel.

To make sure you get what you prescribe, you must check the addition by reversing the prescription in the Lensometer instrument and checking the power of the lens through the segment as compared with the power of the lens at an equal distance above the optical center. This will enable you to determine if the plus lens you prescribed for an addition is duplicated in the Rx.

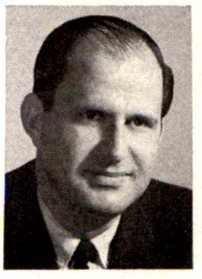
When improperly checked, the power of the addition can vary anywhere from .09D to .37D from what your Rx called for (depending upon the power and thickness of the distance lens).

It's inconvenient to reverse the lens to determine the power of the addition. But it's the only way to determine the true value of the Rx. And it's the *only* way to make sure that your patient gets the quality lens that you prescribed.

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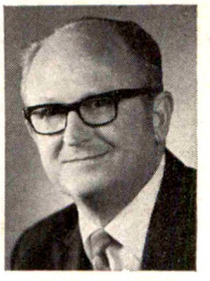
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Recognizing this need, we have formed UNION OPTICS CORPORATION, comprising a select group of established laboratories under the leadership of respected contact lens authorities. This organization is now the second largest contact lens manufacturing entity in the U.S.A. We expect it to play a major part in research, development and improvement of contact lenses in the future.

If you are not yet acquainted with our laboratories, we invite you to get in touch with the one nearest you.

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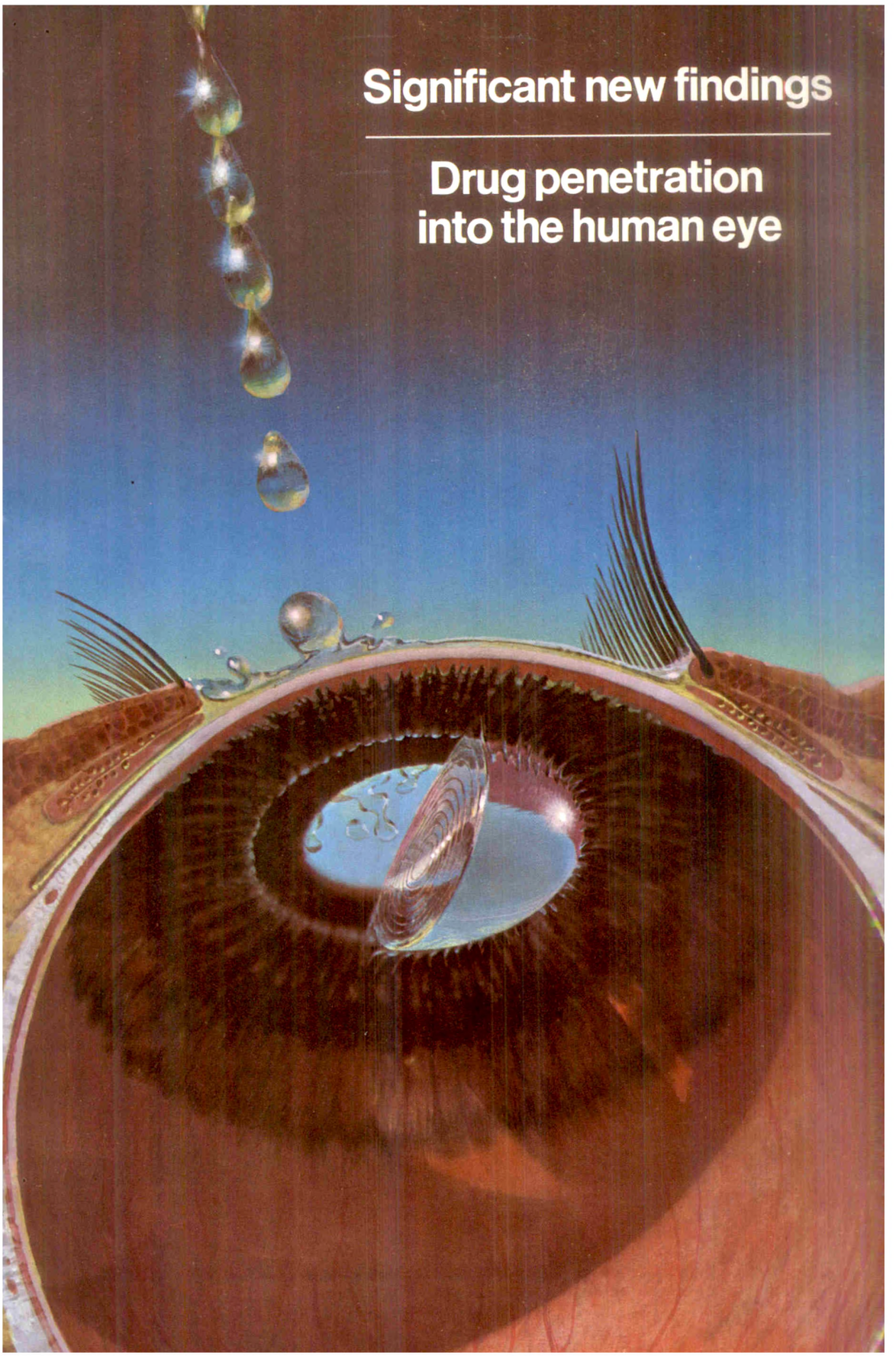
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Significant new findings
Drug penetration
into the human eye

# for the first time independent research relates ocular drug penetration in humans to your choice of ophthalmic vehicles

## Proof of penetration—new fluorophotometry concentration/duration study[1]

Using a slit lamp fluorophotometer, "the effects of ophthalmic vehicles on the intraocular penetration of topical fluorescein in man" were determined. "Quantitative data on ocular penetration of this drug, in man, in vivo are presented."

### The study

Fluorescein combined with hydroxypropyl methylcellulose 0.5%, polyvinyl alcohol 1.4% and aqueous; each vehicle instilled in the eyes of 20 normal subjects; each subject served as his own control; hourly measurements of attained drug concentration were made quantitatively using a slit lamp fluorophotometer.

### The findings

CORNEA

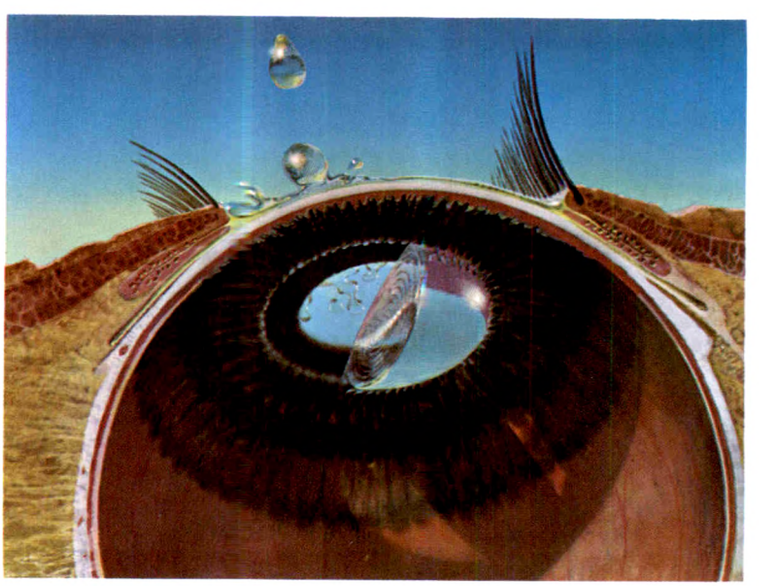
Over a three hour period, hydroxypropyl methylcellulose produced corneal drug levels 85% higher than polyvinyl alcohol and 43% higher than the aqueous vehicles.‡

AQUEOUS HUMOR

Over a three hour period, hydroxypropyl methylcellulose produced aqueous humor drug levels 93% higher than polyvinyl alcohol and 42% higher than the aqueous vehicle.‡‡

### The authentication

The authors state that their findings may, or may not, be true for drugs other than fluorescein. However, the findings reported above were achieved "consistently and reproducibly"; data were analyzed and tested for significance on a computer.



# ...all pilocarpines are *not* the same
# **Isopto® Carpine**
# provides measurably greater response

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demonstrably greater miosis[2]

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because the ISOPTO® vehicle

resists tear dilution and drug washout[3]

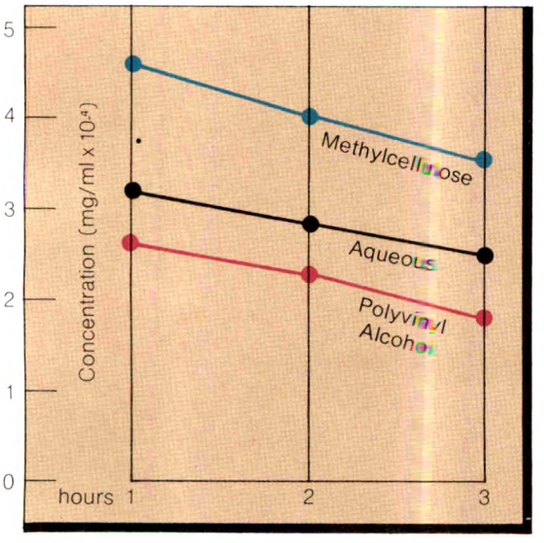
sustains tissue contact[1,4]

increases intraocular penetration[1]

Isopto® vehicle (hydroxypropyl methylcellulose 0.5%)
produced significantly higher drug penetration and concentration
compared with 1.4% polyvinyl alcohol or aqueous vehicles.

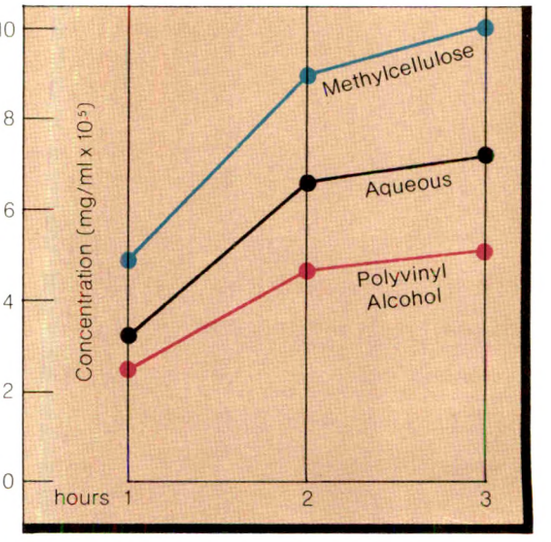
‡Concentration in human cornea

Corneal fluorescein concentration after topical
2% fluorescein in various vehicles




‡‡Concentration in human aqueous humor

Aqueous humor fluorescein concentration after
topical 2% fluorescein in various vehicles.

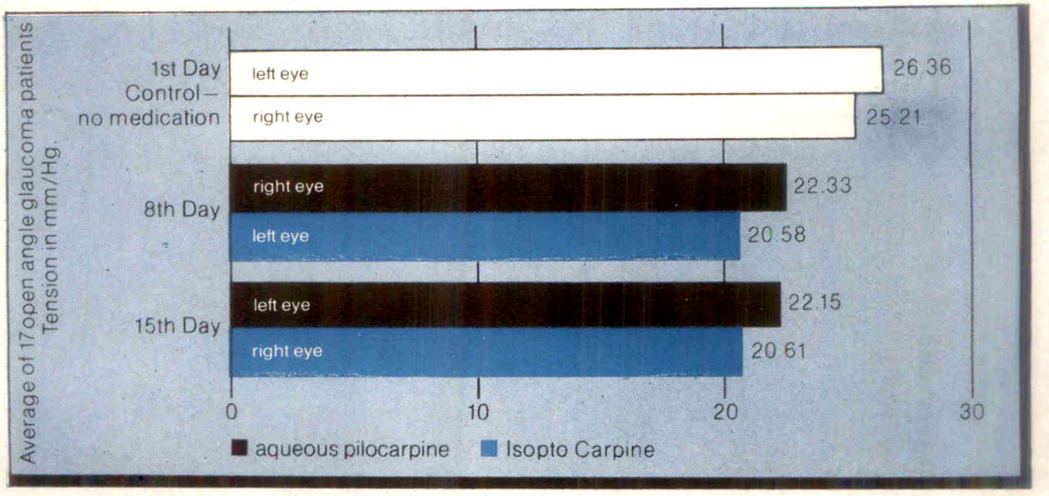



Adapted from Waltman, S.R. and Patrowicz, T.C. Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

...therefore, when penetration makes the clinical difference

# Proven Performance

Study of open angle glaucoma patients shows the clinical difference in vehicles




Adapted from Haas, J.S., and Merrill, D.L.:
The effect of methylcellulose on responses to solutions of pilocarpine, Amer. J. Ophthal. 54:21, 1962.

Results: Significantly greater lowering of IOP with hydroxypropyl methylcellulose solution of pilocarpine (Isopto®Carpine) as compared to aqueous pilocarpine.


**References:**

1. Waltman, S.R. and Patrowicz, T.C.: Invest. Ophthal. *9*:966, 1970.
2. Haas, J.S. and Merrill, D.L.: Amer. J. Ophthal. *54*:21, 1962.
3. Linn, M.L. and Jones, L.T.: Amer. J. Ophthal. *65*:76, 1968.
4. Allen, J.H.: Principles of Treatment of Infectious Diseases of the Lids, Conjunctiva and Cornea, Miss. Doctor, Aug. 1954.


**Description:** Sterile solution containing: Active: Pilocarpine Hydrochloride 0.25%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 8%, or 10%; Vehicle: Hydroxypropyl Methylcellulose 0.5%; Preservative: Benzalkonium 0.01% (0.004%, and Phenylmercuric Nitrate 0.00133% in 0.25% and 0.5% strengths); Inactive: Boric Acid, Sodium Chloride (in 1% only), Sodium Citrate, Citric Acid (in 0.25% and 0.5% only) to adjust pH, Purified Water. **Contraindication:** When constriction is undesirable such as in acute iritis. **Warning:** Rare systemic reactions. **Precaution:** Avoid overdose. **Adverse Reactions:** Slight ciliary spasm with temporary reduction in visual acuity. Sensitivity is infrequently observed. Contact allergy may occur with prolonged use.

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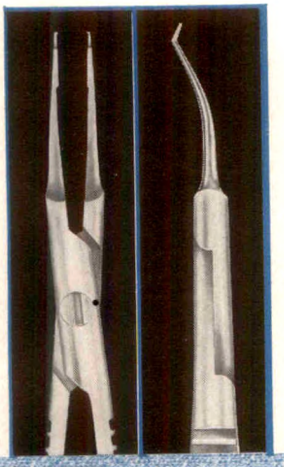
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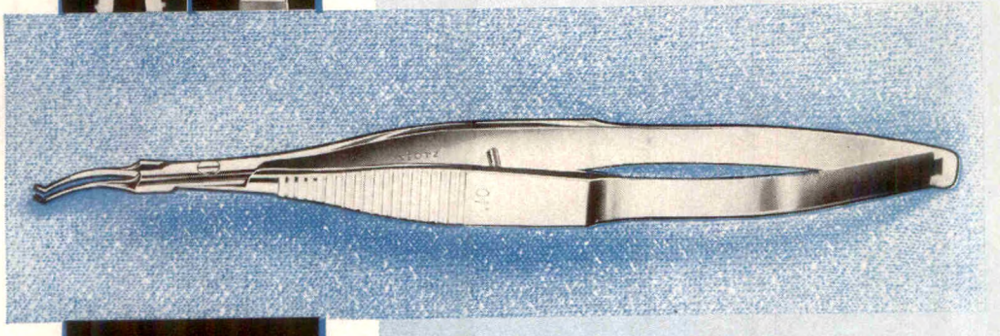


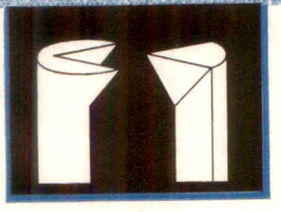
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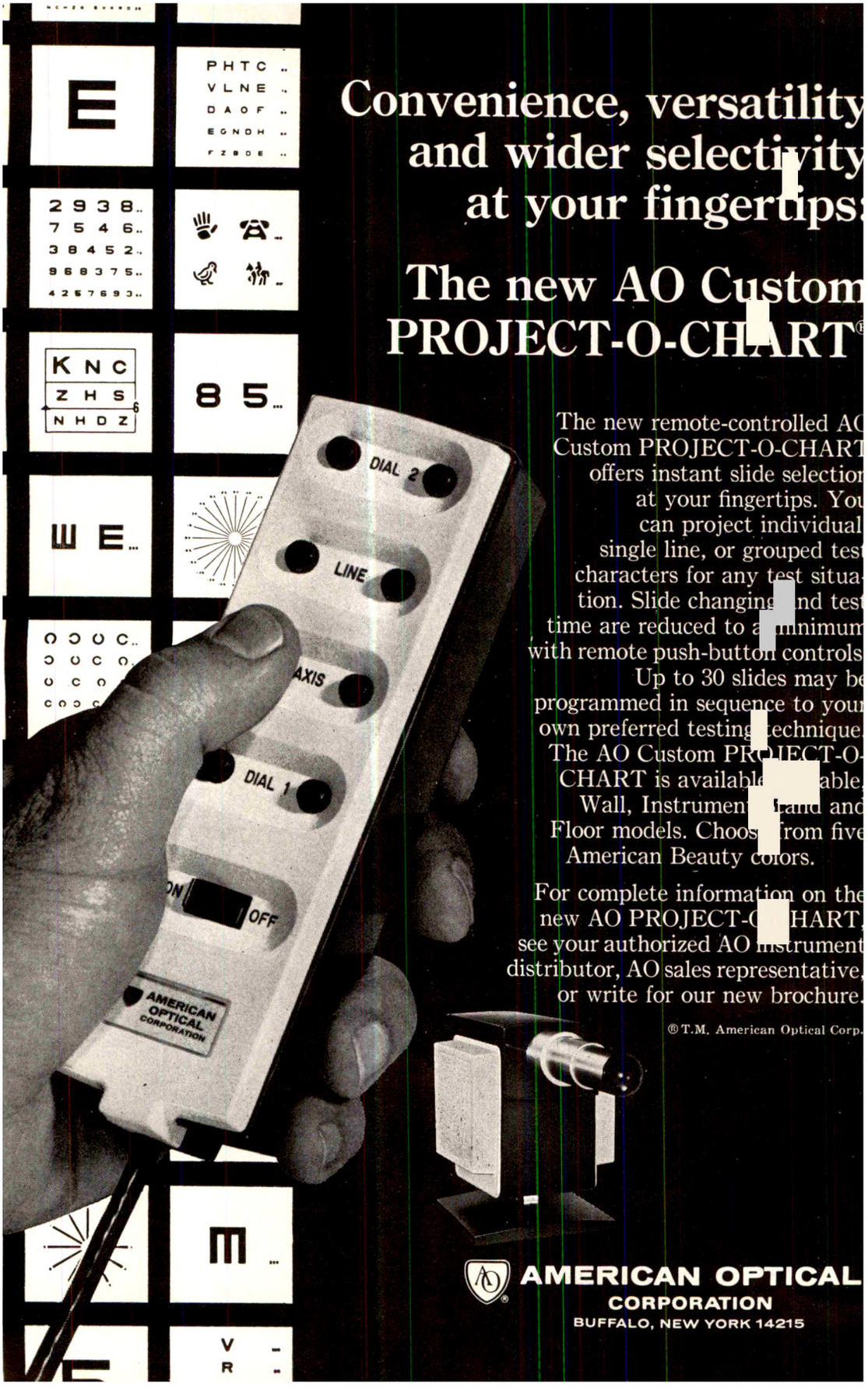
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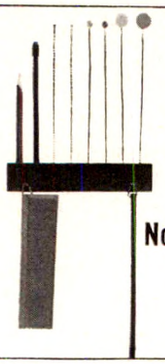
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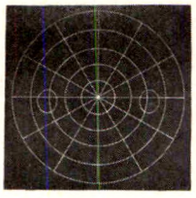
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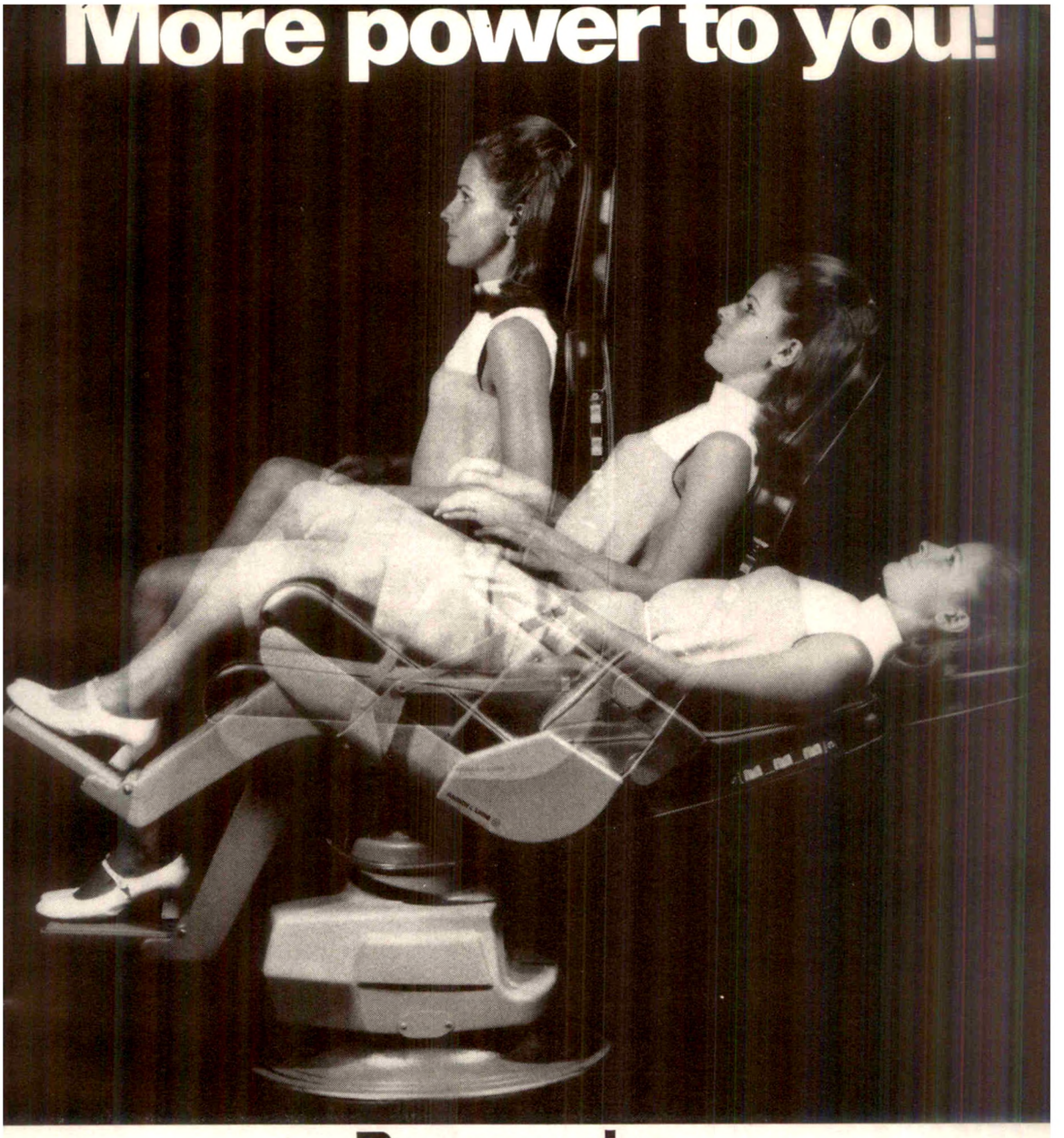
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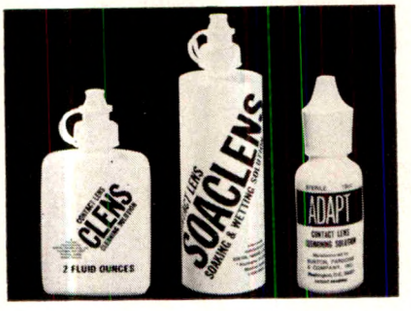
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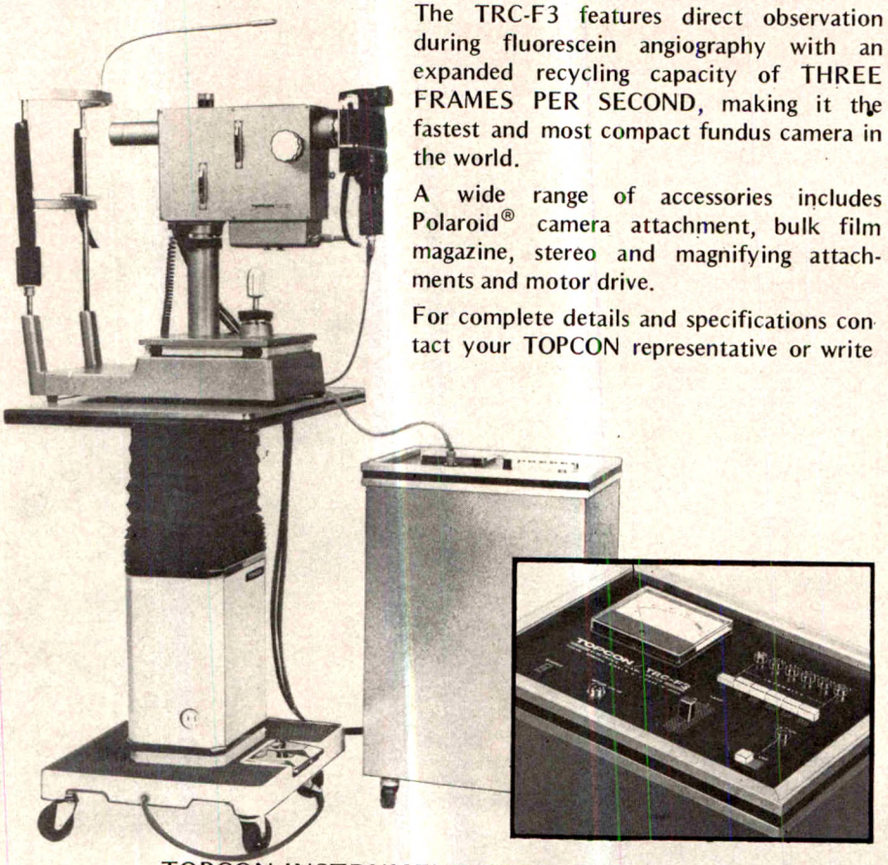
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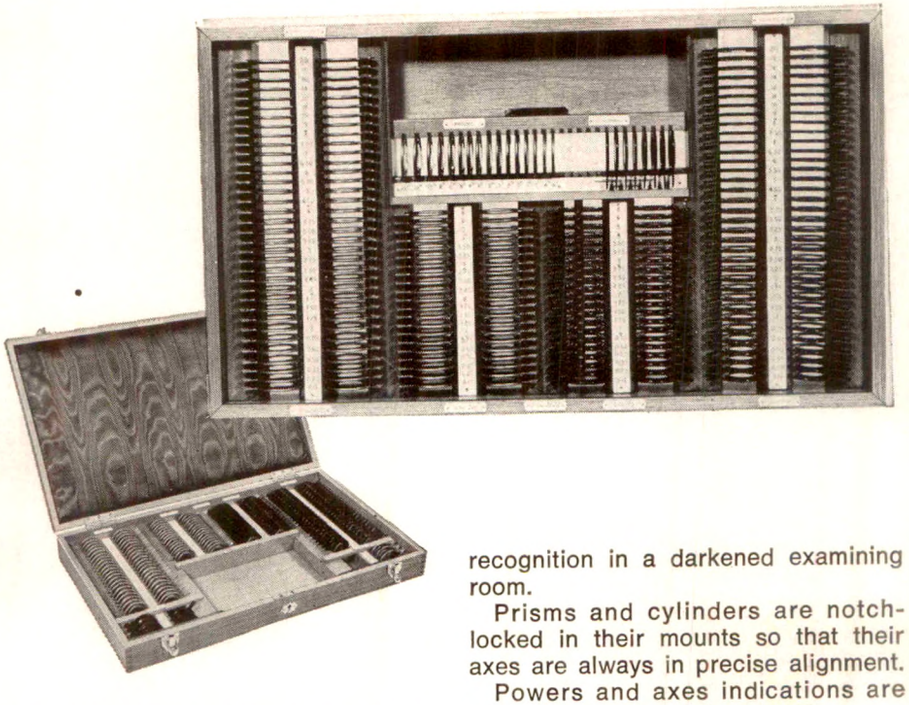
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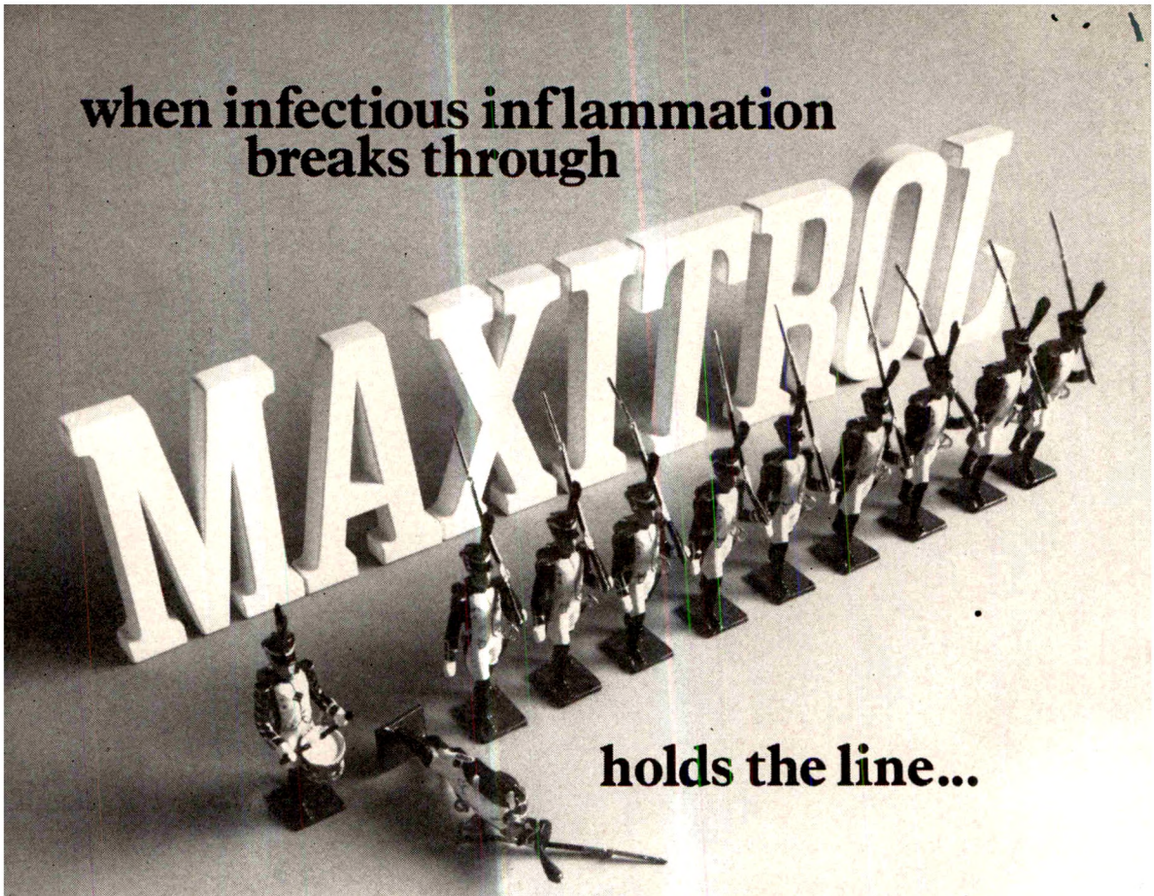
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DESCRIPTION: *DROPS*—Sterile suspension containing: *Active:* Dexamethasone 0.1%, Neomycin (present as sulfate) 3.5mg/cc, Polymyxin B Sulfate 6000 units/cc; Vehicle: Hydroxypropyl Methylcellulose 0.5%; *Inactive:* Sodium Chloride, Polysorbate 20, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), Purified Water; Preservative: Benzalkonium Chloride 0.004%. *OINTMENT—Active:* Dexamethasone 0.1%, Neomycin Sulfate equivalent to 3.5mg/gm Neomycin; Polymyxin B Sulfate 6000 units/gm; *Inactive:* White Petrolatum, Anhydrous Liquid Lanolin; Preservatives: Methylparaben 0.05%, Propylparaben 0.01%. CONTRAINDICATIONS: This drug is contraindicated in tuberculous, fungal, and most viral lesions of the eye (herpes simplex/dendritic keratitis); vaccinia, varicella; acute purulent conjunctivitis and acute purulent blepharitis, and in those persons who have shown hypersensitivity to any of its components. PRECAUTIONS: Extended use may cause increased intraocular pressure which should be checked frequently and may result in overgrowth of nonsusceptible organisms. Perforation can occur in diseases causing thinning of the cornea. Discontinue use if sensitivity occurs. Not recommended for long-term use in pregnant patients.

References: 1. Nelson, E. L.: "Ophthalmic Steroids," in Kaufman, H. E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970. 2. Waltman, S. F. and Patrowicz, T. C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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# A MODIFIED TECHNIQUE OF EXTERNAL DACRYOCYSTORHINOSTOMY

FIRST AMERICAN JOURNAL OF OPHTHALMOLOGY LECTURE

PAN AMERICAN ASSOCIATION OF OPHTHALMOLOGY

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*San Juan, Puerto Rico*

In 1966, Dr. William A. Mann performed a valuable service to us all by preparing a detailed—and most interesting—history of The American Journal of Ophthalmology[1] from its origin in 1884 to the present. This is, beyond question, one of the most distinguished medical journals of the world, and one of its most important accomplishments is the contribution it has made to the development of close scientific and personal relations among ophthalmologists of the Americas, particularly through the Pan American Association of Ophthalmology. As I speak these words, many names come to my mind, as I am sure they come to yours. Among them are:

Dr. Manuel Uribe Troncoso, who served on the editorial board of the Journal for 40 years, from 1918 to 1958.

Dr. Harry Gradle, who served on the editorial board from 1929 to 1949, and who was responsible for the foundation of the Pan American Association of Ophthalmology in 1934.

Dr. Derrick T. Vail, who was editor of the Journal from 1940 to 1965.

Dr. Frank W. Newell, who has been editor of the Journal since 1965, and who has continued its traditional support of the Pan American Association of Ophthalmology, to the great betterment of this specialty throughout the Americas.

Dr. Newell and his editorial board conceived the idea of an American Journal of Ophthalmology Lecture, the first of which I have the honor to deliver today and which will be delivered every second year hereafter. These lectures will, of course, be published in the Journal.

I cannot find what Kipling once called "the magic of the necessary word" to express my gratitude to the committee from the Pan American Association and the editorial board of the American Journal of Ophthalmology for selecting me to deliver the first of these lectures. Believe me, I feel the responsibility as well as the honor of the selection, for, as I conceive it, they are symbols of the scientific union among the United States of America, the Americas to the south, and Canada. I might add that I am particularly gratified that the educational endeavors in which I am so vitally interested played some part in the honor that has come to me.

## GENERAL CONSIDERATIONS OF SURGERY IN DACRYOCYSTITIS

I have elected to speak to you today on a procedure for the relief of dacryocystitis for several reasons:

1. I am frequently called upon to produce this relief. I have no statistical proof, but it is my impression that this condition is more

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common in the tropics than in more temperate regions.

2. Dacryocystitis is always a source of annoyance and discomfort to the patient, and not infrequently the epiphora is disabling.

3. The necessity of surgery for this condition is not always appreciated. Once it has become established in adults, medical management, including potent antibiotic therapy, is futile; the epiphora, which is the patient's chief concern, will continue. In children, dacryocystitis is usually the result of congenital stenosis of the nasolacrimal duct. Probing, though it should be tested, is generally ineffective after the age of three years and the operation should be performed at that age or shortly thereafter.

4. Finally, for some reason which has always eluded me, even competent ophthalmic surgeons are often not equipped, either by training or experience, to perform the surgery required in dacryocystitis. For many years, both as a practicing ophthalmologist and as a teacher, I have been disturbed by the fact that so many otherwise highly competent ophthalmic surgeons, who are well skilled in other procedures, are so inept—I use the word deliberately—when they are faced with surgical problems of the lacrimal drainage system. Perhaps the principal explanation for this situation is that many of the procedures advocated for them are so difficult technically and so prone to complications that the average surgeon becomes frustrated and drops them from his armamentarium.

I must confess that I myself would never have become interested in dacryocystorhinostomy if:

1. I had to deal with the excessive bleeding from the nasal mucosa and the angular blood vessels that occurs when precautions are not taken to prevent it.

2. I had to perform the operation in the restricted space available to working without the separation of the medial canthal tendon from its insertion at the anterior lacrimal crest.

3. The difficult suturing of two flaps of nasal mucosa to two flaps of lacrimal sac were necessary in the technique I employ, as it is in the Dupuy-Dutemps operation.

## Historical note

I have made no comprehensive review of the literature for this presentation, but I think my remarks will be clearer if I begin with a brief historical note on dacryocystorhinostomy. Its origin, according to Chandler,[2] dates from the time of Celsus, in the first century of the Christian era. Galen, in the second century, also employed surgery to create a new passageway from the lacrimal sac into the nose. Other details of the first use of this operation can be found in Chandler's article, as well as in other excellent articles by Arruga[3] and by Welt.[4]

Modern surgery of the lacrimal sac began in Italy, in 1904, with Toti's[5] description of an operation which involved (1) creation of an opening into the nasal wall with hammer and chisel, and (2) removal of the nasal mucosa in this opening and the medial half of the lacrimal sac. Sutures were used only in the skin. Toti was successful in about half of his cases. Blascovics,[6] in 1912, used the Toti technique but removed the entire lacrimal sac except for a small portion surrounding the opening of the canaliculi.

Thereafter, the basic technique of dacryocystorhinostomy was successively modified as follows:

In 1914, Kuhn[7] cut the nasal mucosa in horseshoe fashion, leaving it attached anteriorly and suturing it to the periosteum anterior to the bony opening.

In 1921, Mosher[8,9] combined the Toti technique with intranasal removal of the tip of the middle turbinate and suture of the anterior border of the opening in the lacrimal sac to the tissues anterior to the bony opening. He anticipated success in 90% of all cases. In 1947, Hogan[10] reported such results in 49 operations performed by a modification of the Mosher-Toti technique.

In 1920, and again in 1922, Dupuy-Du-

temps and Bourguet,[11,12] in France, and in 1921, Ohms,[13] working independently in Germany, modified the Toti technique by dissecting the anterior and posterior flaps of the nasal and lacrimal mucosa and then suturing the flaps together. The French surgeons had successful results in 94.8% of more than 1000 operations. Since then a number of other observers[2,4,14-18] have reported large series of operations performed by this technique with success rates ranging from 85 to 100%.

In 1925, Basterra[19] modified the Dupuy-Dutemps technique by dissecting an anterior flap of nasal mucosa and suturing it to the anterior border of the opening in the lacrimal sac.

In 1944, Soria[20] recommended suturing a single flap of nasal mucosa to the posterior flap of the lacrimal sac. He also recommended suturing the anterior flap of the sac to the anterior border of the bony opening. Gauze drainage from the sac down to the nasal fossa was provided for 72 hours.

In 1911, Forsmark[21] recommended transplantation of the lacrimal sac. The same recommendation was made by Stock[22] in 1934 and by Gifford[23] in 1944. In this technique the sac is severed from the nasolacrimal duct at its junction with it, after which its lower end is pulled into the bony nasal opening by sutures brought out through the nostril.

In 1946, Arruga[3] brought together his experiences with dacryocystorhinostomy, which covered many years and which had previously been reported in a number of publications. His operations were performed by the Dupuy-Dutemps technique and were facilitated by several new instruments of his own design. He also described a technique for dacryocystorhinostomy applicable to patients who had previously undergone dacryocystectomy.

In 1954, Iliff[24] suggested that the Stryker saw be used to open the lateral bony nasal wall. This was a very helpful suggestion. The use of this instrument simplifies the technique, shortens the operating time, and diminishes the former risk of damage to the soft tissues. The rapid oscillating action of the saw is far less traumatic than the action of dental or other burs, bone chisels, and rongeurs.

In what has been said so far in this brief historial note one must be impressed by the many efforts made to modify the Dupuy-Dutemps technique. The reason, it seems, is that this is a difficult operation, particularly in respect to the accurate approximation of the corresponding flaps of nasal mucosa and lacrimal sac by direct sutures. Another reason for failure in a certain number of cases is postoperative closure of the newly created lacrimal tract, either by formation of granulation tissue at the new bony opening or by adhesion of the anterior flaps to the posterior flaps. Arriaga[25] puts particular stress on this latter possibility. To simplify the operation, several observers recommend that no sutures be used to unite the flaps but instead, plugging agents should be left between them.[24,26] Other surgeons use the basic Dupuy-Dutemps technique or some modification thereof and suture the flaps, but also leave some sort of plugging agents between them (rubber catheters, steel wire, silicone sponges, polyethylene tubes, umbilical tape, and wicks of suture material and gauze).[17,25,27-32]

To bring this resume to a close, in 1958, and again in 1963,[33,34] I myself presented a technique of external dacryocystorhinostomy, based in part upon the operation described by Ramón Castroviejo in 1942,[35] and itself a modification of the Dupuy-Dutemps technique. The flaps are sutured as recommended by Soria.[20] The bony opening is created by the Iliff trephine on the Stryker saw.[24] A 2-0 or 4-0 silk suture is left in the new lacrimal drainage pathway for several days, as recommended by Castroviejo.[35] I have used this technique over the past several years and have found it simple, safe, efficient, and uncomplicated. Absence of bleeding, when it is properly performed, is one of its most desirable features.

## Indications and preoperative measures

Useful as dacryocystorhinostomy is, dacryocystectomy is still indicated in three diseases of the lacrimal sac—namely, malignant lesions, tuberculosis, and syphilis. This operation was formerly the favored procedure for all conditions of the lacrimal sac, but now it has been almost entirely replaced by external dacryocystorhinostomy. Dacryocystorhinostomy takes a little longer to perform, it is true, which is undesirable in older patients, and it is somewhat more traumatic than simple excision of the sac, but these disadvantages are more than compensated for by the better end results.

If a chronic dacryocystitis must be corrected before intraocular surgery, dacryocystorhinostomy is the preferred operation. Even if the epiphora that tends to persist after the excision operation is not severe, stagnation of tears in the conjunctival sac can create a dangerous, persistent infection that may complicate any subsequent intraocular procedure.

Dacryocystorhinostomy is also indicated for the relief of disabling epiphora due to physiologic insufficiency of the lacrimal pump or to atonic distension of the lacrimal sac.

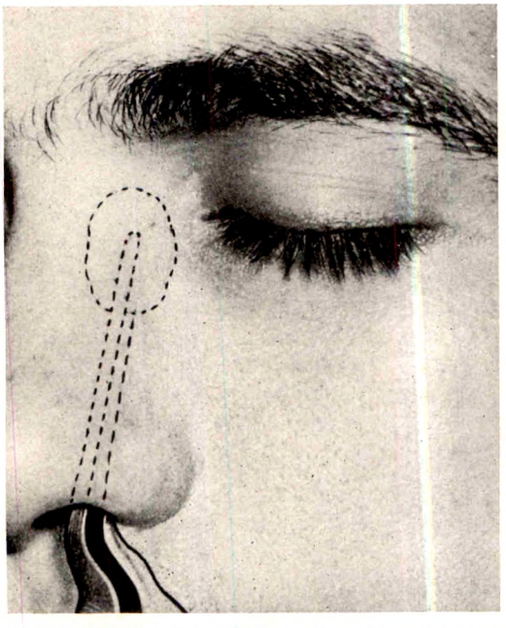


Fig. 1 (Picó). Introduction of moistened cotton tampon into nose.

The surgeon who undertakes any operation on the lacrmial sac must possess a precise knowledge of the anatomy of the lacrimal excretory pathways and of their relations to other structures and landmarks. Bleeding will be excessive and dangerous, for instance, unless the surgeon bears in mind the position of the angular blood vessels, which are situated slightly anterior to the anterior lacrimal crest.

Preoperative dacryocystography may give valuable information. Two other preoperative precautions are important: Patency of the lower punctum, the common punctum, and the canaliculus must be assured, and good illumination must be provided, preferably with a Lempert head lamp.

## Technique of external dacryocystorhinostomy

*Anesthesia*—The best results in external dacryocystorhinostomy are obtained with general anesthesia supplemented by local anesthesia applied to the nasal mucosa and the superficial tissues over the lacrimal sac as follows:

A cotton tampon, well saturated with equal quantities of cocaine solution (4%) and epinephrine (1:1000) is introduced into the nose and brought into contact with the area of nasal mucosa which corresponds to the lacrimal fossa (Fig. 1). A length of thread attached to this tampon facilitates its later removal at the appropriate stage of the procedure. The shrinkage and ischemia which follow this application inhibit bleeding when the mucosa is incised.

The superficial tissues over the lacrimal sac are injected with 3 ml of procaine HCl solution, to which two drops of epinephrine (1:1000) have been added.

*Incision*—A vertical incision, 3.5 cm long, is made 3 mm medial to the inner canthus, through the skin and subcutaneous tissues up

to the medial canthal tendon (Fig. 2). A Stevenson lacrimal sac speculum is introduced into the incision.

An incision in this location carries with it no risk of damage to the angular blood vessels situated slightly anterior to the anterior lacrimal crest. As just pointed out, the surgeon who does not keep in mind the position of these vessels is likely to find himself confronted with excessive and dangerous bleeding.

*Steps of the procedure*—External dacryocystorhinostomy is performed in the following steps:

1. The medial canthal tendon is cut with scissors close to its insertion at the anterior lacrimal crest (Fig. 3), after which the overlying periosteum is incised with a knife and is separated anteriorly with a periosteal elevator, a step which leaves the bone bare. This technique, it must be admitted, is controversial.

Most descriptions of dacryocystorhinostomy in the American literature, contrary to those in the European literature, insist that the medial canthal tendon be left attached at its insertion and that the operation be carried out below the lower edge of this tendon. My experience has been that such a technique makes the operation more difficult because of the restricted area in which the work must be done, and that it is important, in the interest of visibility, to separate the medial canthal tendon from its insertion.

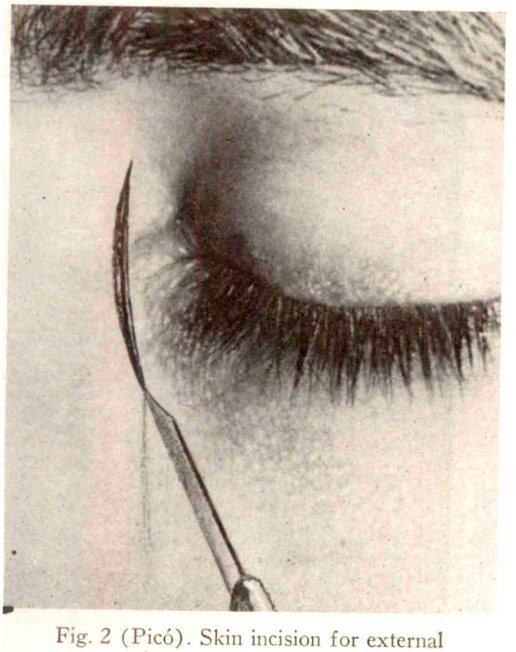


Fig. 2 (Picó). Skin incision for external dacryocystorhinostomy.

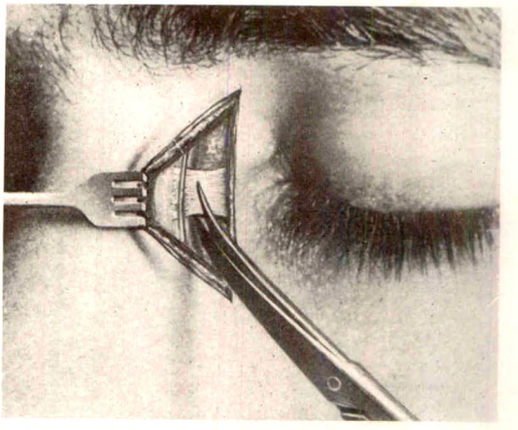


Fig. 3 (Picó). Division of medial canthal tendon. Note that the angular blood vessels are located just anterior to the insertion of this tendon.

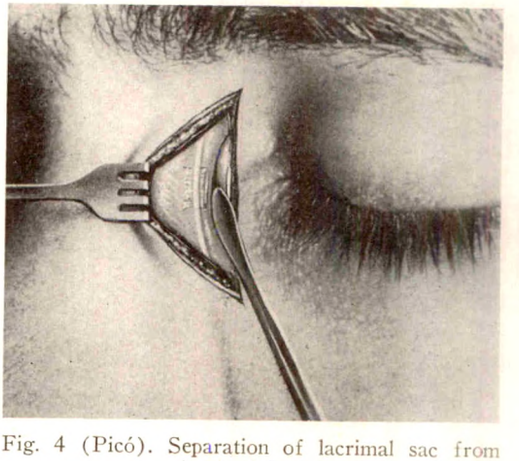


Fig. 4 (Picó). Separation of lacrimal sac from lacrimal fossa.

2. The lacrimal sac, which is located in the lacrimal fossa immediately posterior to the canthal tendon, is dissected free laterally from the fossa (Fig. 4). The periosteum is also separated from the fossa.

3. The Stevenson lacrimal sac speculum is

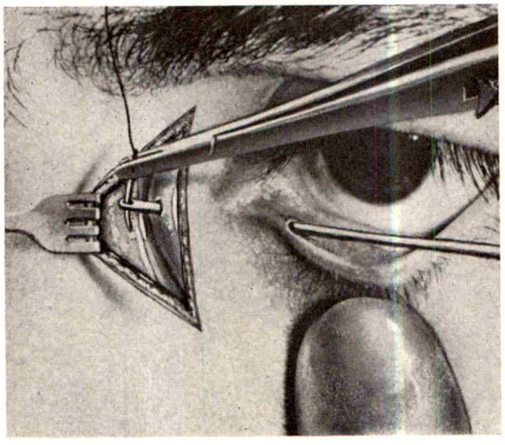


Fig. 5 (Picó). Passage of silk suture through Castroviejo probe after passage of probe through canaliculus and lacrimal sac.

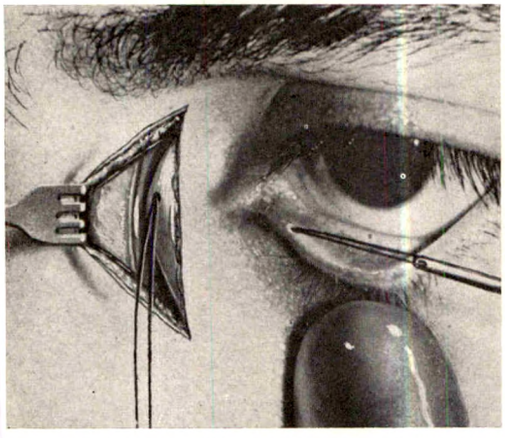


Fig. 6 (Picó). Withdrawal of probe with suture.

now removed from the incision. A special Castroviejo probe, with an opening in the tip, is passed through the lower canaliculus and into the lacrimal sac and then is pushed further through the medial wall of the sac.

4. A needle threaded with 2-0 or 4-0 silk suture is passed through the opening in the Castroviejo probe (Fig. 5). One end of this suture is brought out through the canaliculus and punctum lacrimale by withdrawing the probe (Fig. 6).

5. An opening is made in the nasal bony wall with the 10 mm Iliff trephine on the Stryker saw (Fig. 7). The trephine is so placed on the anterior lacrimal crest that a third of the opening is anterior to the crest and two-thirds is posterior to it. The center of the opening is at the level of the common punctum. Removal of the bone exposes the nasal mucosa (Fig. 8). If the ethmoidal cells are entered in this step of the procedure, as occasionally happens, they should be removed with forceps until nasal mucosa is exposed.

6. A flap of nasal mucosa is dissected along the border of the bony opening but is left attached posteriorly (Fig. 9). In an occasional case the tip of the middle turbinate is found to be encroaching on the bony opening and must be excised with the rongeur or forceps.

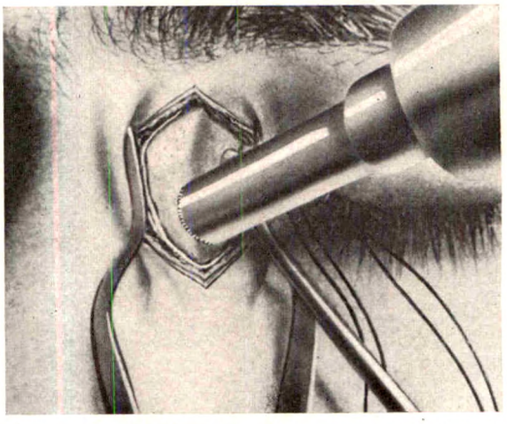


Fig. 7 (Picó). Creation of bony opening with 10 mm. Iliff trephine of Stryker saw.

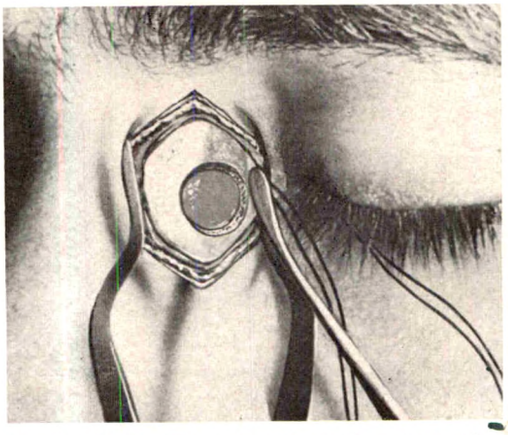


Fig. 8 (Picó). Exposure of nasal mucosa after removal of piece of bone.

7. The cotton tampon in the nasal cavity is removed.

8. A vertical incision is made in the nasal aspect of the lacrimal sac by introducing Westcott scissors through the opening previously made in the medial wall of the sac; anterior and posterior flaps of sac are thus created (Fig. 10). I join a number of other surgeons (Hallum,[17] McPherson,[18] Callahan,[30] and Werb[36]) in warning the surgeon to be certain at this point that the wall of the lacrimal sac has been completely opened and the lumen has been reached and exposed.

9. The posterior flap formed from the lacrimal sac is sutured to the flap formed from the nasal mucosa. A spatula type of needle is used to introduce three sutures of 4-0 chromic catgut (Fig. 11). In the technique I am describing this step is carried out without the difficulty experienced in the Dupuy-Dutemps technique because the single flap which I employ is larger than the posterior flap used in the Dupuy-Dutemps technique.

10. The other end of the silk suture in the

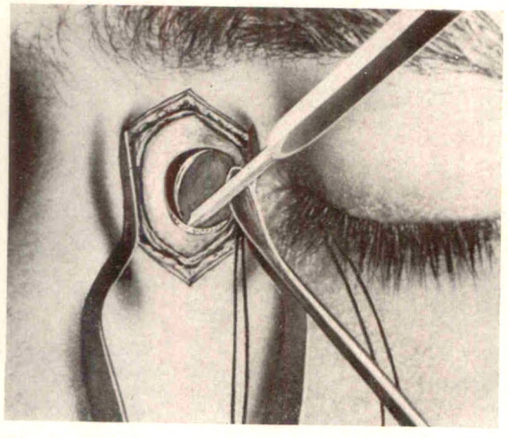


Fig. 9 (Picó). Dissection of flap of nasal mucosa.

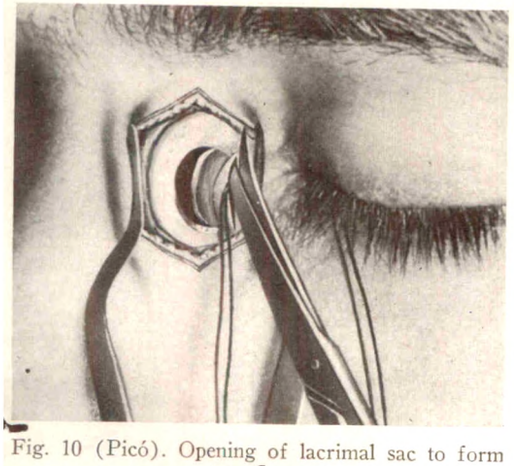


Fig. 10 (Picó). Opening of lacrimal sac to form two flaps.

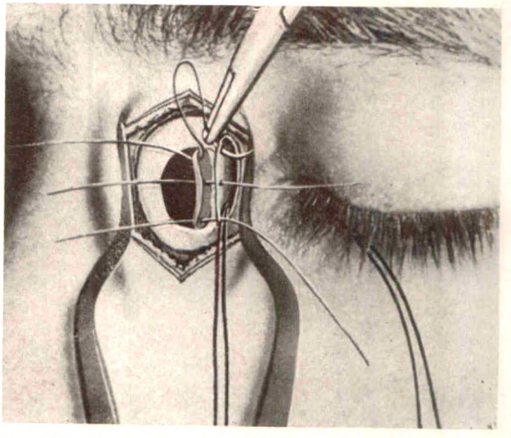


Fig. 11 (Picó). Suture of flap of nasal mucosa to posterior flap of lacrimal sac.

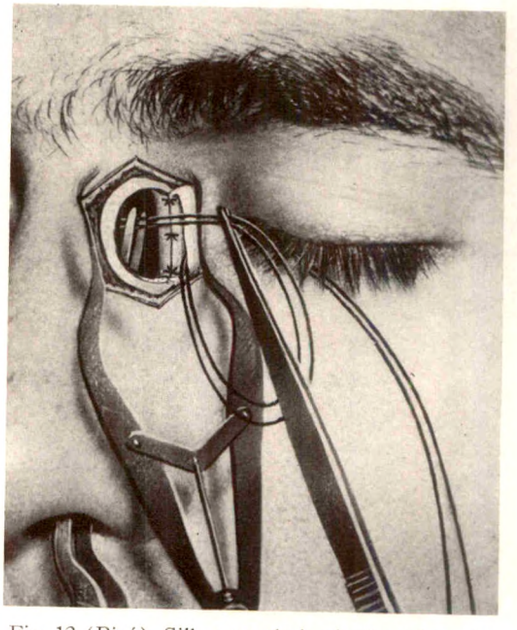


Fig. 12 (Picó). Silk suture in lacrimal sac brought down outside of nose.

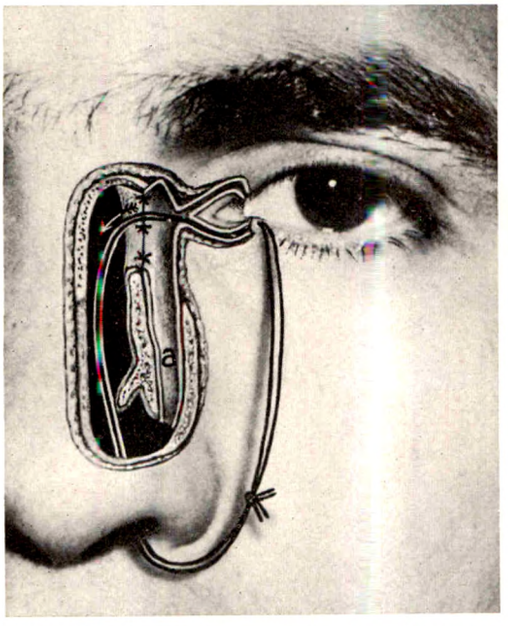



Fig. 13 (Picó). Diagram showing silk suture passed through new pathway and down nasal cavity to exterior.

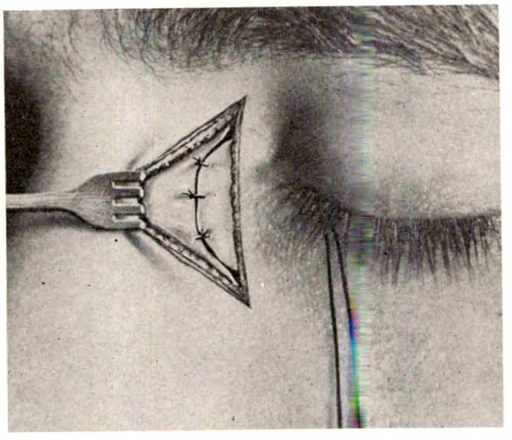


Fig. 14 (Picó). Suture of anterior flap of lacrimal sac to periosteum anterior to bony opening.

lacrimal sac is brought down outside the nose (Fig. 12) and is tied to the end already brought out through the punctum (Step 4, Fig. 13).

*Closure of wound*—The anterior flap of the incised lacrimal sac is sutured to the periosteum that was retracted anterior to the bony opening with three sutures of 4-0 chromic catgut. The medial canthal tendon is reattached without direct sutures; there is no need for them because the tendon will be displaced nasally when the anterior flap of the lacrimal sac is sutured to the periosteum anterior to the bony opening (Fig. 14). Additional sutures are used to approximate the subcutaneous tissues.

The skin is closed with a continuous 6-0 silk suture (Fig. 15). Finally, a light dressing is applied.

*Dacryocystorhinostomy after dacryocystectomy*—If the patient has already undergone dacryocystectomy, it may still be possible to perform dacryocystorhinostomy, though only if the lower canaliculus is patent. Two flaps of the fibrous tissue that has replaced the lacrimal sac are used instead of the two flaps of lacrimal sac used in the basic operation. One of the flaps of fibrous tissue is anterior to the common punctum and the other is posterior to it. The anterior flap is attached to the periosteum that was retracted anterior to the bony opening and the posterior flap is attached to the single flap of nasal mucosa. Otherwise, the usual technique is followed.

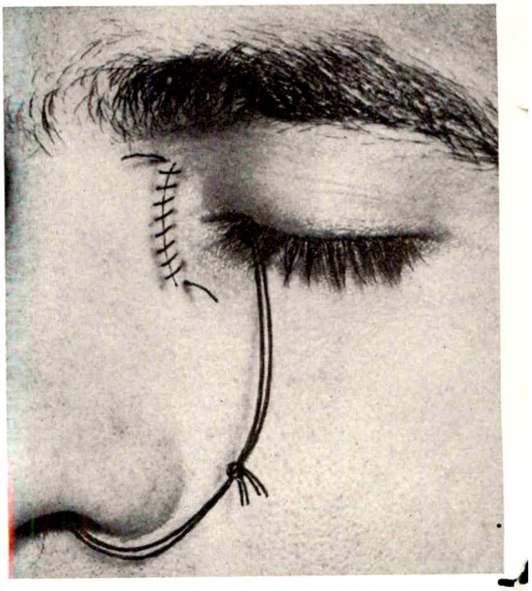


Fig. 15 (Picó). Closure of skin by continuous silk suture.

*Postoperative management*—Dressings are changed every second day. Each time the eye is dressed the silk suture in the newly created nasolacrimal passage is moved toward the nose in order to dislodge any granulation tissue or blood clot that might be present in the bony opening.

Both the silk suture in the nose and the skin suture are removed on the seventh postoperative day. The new lacrimal passage is irrigated at the end of the second postoperative week and at weekly intervals thereafter for the next four weeks.

## Analysis of cases

### Material and methods

The material on which this presentation is based consists of 121 consecutive external dacryocystorhinostomies performed between 1963 and 1969 for chronic dacryocystitis with epiphora and obstruction of the nasolacrimal duct. Sixteen of the patients had histories of acute attacks.

Ninety-one of these operations, 10 of which were bilateral, were performed at the Puerto Rico Medical Center by members of the house staff. Each operation was supervised by a member of the attending staff, who acted at it as first assistant. The other 30 operations, five of which were bilateral, were performed in my private practice.

All these patients were followed for at least six months and most of them were observed for over a year. The operation was considered successful if epiphora was eliminated and normal irrigation through the new drainage channel was possible.

Over the 1963–69 period, in addition to the 121 operations (15 bilateral) performed by the technique just described, 10 other operations were performed for this condition by other techniques. The data in these cases are included in the age and sex incidence to be discussed shortly.

### Results

By the criteria just laid down there were only four failures in these 121 operations, three in the public hospital cases and the other in my private practice. One of these patients had had a previous dacryocystectomy elsewhere. In every instance the cause of the failure was found at secondary surgery to be an obstruction of the new drainage channel by an occluding membrane, which histologic examination showed to be composed of organized granulation tissue.

Secondary surgery, which was successful in all four cases, consisted of removing the obstructing membrane by opening the anterior wall of the new pathway and exposing the bony opening.

### Complications

*Anatomic complications and their management*—Anatomic complications encountered at operation consisted of:

1. Total absence of the lacrimal sac because of previous dacryocystectomy (three cases) and small sacs (four cases). In either of these circumstances, adequate anastomosis of a single flap of nasal mucosa to a small posterior flap of lacrimal sac is usually possible, or the anastomosis can be accomplished by use of the small remnant of lacrimal sac mucosa left around the common punctum after a previous dacryocystectomy.

2. Thinning and atrophy of the nasal mucosa (one case). In such cases it is usually possible to dissect a single flap and suture it to the posterior flap of the lacrimal sac.

3. Distortion of the bony anatomy caused by the presence of ethmoidal cells in the area of trephination (three cases). In such cases the thin bony walls and the mucosal lining of the cells must be removed with strong forceps until true nasal mucosa is reached.

4. Encroachment of the top of the middle turbinate on the bony opening (one case). Excision of the tip solves this problem.

5. Obstruction at the common punctum (one case). When a stricture is present in this location as part of the chronic dacryocystitis (it may not appear until weeks or even months later), the operation should be concluded by leaving a Veirs rod in the lu-

men of the canaliculus, the common punctum and the newly created lacrimal drainage passageway for six weeks.

6. Fistulas of the lacrimal sac to the skin (two cases). Such fistulas are managed by dissecting them out at operation as part of the skin incision.

7. Tenacious adhesions of the anterior wall of the lacrimal sac to the posterior aspect of the medial canthal tendon (one case). Separation of the adherent structures requires only careful dissection.

None of the 16 complications just described presented any serious difficulties at operation.

*Technical complications*—Complications encountered at operation were few and readily handled. Bleeding occured in five cases. In two instances it originated from the angular vessels and in the other three from the nasal mucosa. In one case the nasal mucosa was accidentally severed while the trephine bony opening was being made.

*Postoperative complications*—Postoperative complications were few. They consisted of serious nasal bleeding (one case), abscess of the skin incision (one case), an unsightly scar (one case), a partial stricture at the common punctum (one case), and obstruction at the bony opening (four cases). An unsightly skin scar can be prevented by use of a rectolinear incision and careful, precise suture of the skin and soft tissues. Strictures can usually be prevented by keeping the silk suture in the nose for at least a week after operation. Dilatation is helpful in late cases. The single instance of stricture in my series was found several weeks after operation and did not occlude drainage. Obstruction of the bony opening was the cause of the four failures.

## Comment

One of the most interesting features of the analysis of the combined series of operations (131 operations on 116 patients) is the sex and age distribution. There were 28 males and 88 females, and the age range was from three to 85 years. Before 20 years of age there was a predominance of males (7). This group included a number of patients with congenital dacryocystitis. After the menopausal years females predominated. Of the 88 female patients, 61 were between 40 and 70 years of age.

The age distribution in these 116 cases corresponds to that reported by McPherson and Egleston[18] and the sex distribution to that reported by Traquair.[37] According to Meller,[38] the lumen of the nasolacrimal duct is narrower in women than in men. If his data are correct, they might also explain the higher frequency of bilateral disease in women. At any rate, the sex differential exhibited in this and other series as related to age suggests a possible endocrine factor in the etiology of dacryocystitis.

The results of these 121 operations, in which there were only four failures, can fairly be considered good. A point in favor of the technique described in this communication is the sameness of the results achieved in the public hospital cases, in which the surgery was done by inexperienced residents, and in my private cases, in which it was done by a surgeon of long experience. Reflection has convinced me that the similarity of results in the two series can be explained by the careful attention paid in both circumstances to the following considerations:

1. The location of the skin incision 3 mm from the inner canthus. This permits precise identification of the angular blood vessels and their careful retraction under direct vision. The incidence of bleeding is thus greatly reduced. It is also reduced by the introduction into the nose, at the beginning of the operation, of a cotton tampon well saturated with cocaine solution and epinephrine.

2. The good exposure achieved by separation of the medial canthal tendon at its insertion.

3. Creation of an adequate bony opening (10 mm) with the Iliff trephine on a Stryker saw.

4. The use of a single flap of nasal mu-

cosa to be sutured to the posterior flap of the incised lacrimal sac, instead of double flaps as in the Dupuy-Dutemps technique.

5. Suture of the flaps, a step essential to good healing. Arruga[3] also emphasizes the importance of this step. He had better results in the operations in which flaps of nasal mucosa and the lacrimal sac were firmly anastomosed by suture. Another point to be emphasized in this connection is that proper fixation of the flaps by suture will prevent occlusion of the new channel by their derangement and collapse.

6. The use of a silk suture in the nose to maintain patency of the new nasolacrimal pathway. Manipulation of this suture every second day dislodges whatever blood clots may be present at the opening and also prevents whatever occlusion of the common punctum might occur as the result of surgical trauma.

7. The constant recollection that the key to the management of complications before and after operation is their prevention.

The four failures in this series were all due to the same cause, obstruction at the bony opening, which itself was due to organized granulation tissue, not to a bony growth. I have come to the conclusion that this complication is inevitable in an occasional case, no matter how precise the technique has been. I am strongly opposed to the use of any foreign materials between the walls of the new anastomosis as a preventive measure. They simply disrupt the suture lines in the flaps, and they may even stimulate the formation of obstructing granulation tissue by causing irritation in the bony opening.

## Summary

A modified technique of dacryocystorhinostomy has been developed for the treatment of chronic dacryocystitis. Important considerations are as follows: Skin incision should be located 3 mm from the inner canthus. The medial canthal tendon must be separated from its insertion. A large single posterior flap of nasal mucosa must be created, and this must be sutured to the posterior flap of the lacrimal sac. The anterior flap of the lacrimal sac must be sutured to the periosteum anterior to the bony opening. Reattachment of the medial canthal tendon must be without direct sutures. Special precautions must be taken to maintain the patency of the newly created nasolacrimal channel. The safety and efficiency of this operation, when it is performed by competent ophthalmic surgeons with a sound knowledge of regional anatomy, are shown by the results in two series of operations totaling 121 cases in which there were only four failures and only one serious complication.

## Acknowledgments

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# SURGICAL TREATMENT OF TRAUMATIC BLEPHAROPTOSIS

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The surgical treatment of acquired blepharoptosis is more complex and the results less predictable than that of congenital blepharoptosis. This is especially true of the traumatic cases; they are relatively rare and no two cases are identical.

## INCIDENCE OF TRAUMATIC BLEPHAROPTOSIS

Less than 2% of all major ophthalmic operations are for blepharoptosis.[1] Reports[2-5] show that tramua was the indication in only 9% of 1109 operations for blepharoptosis (Table 1), and since the incidence of traumatic blepharoptosis is so very low, it is unlikely that any one surgeon can collect enough such cases during an entire lifetime to formulate reliable guidelines for surgical treatment. Nevertheless, I shall propose a simple formula for avoiding gross amounts of overcorrection or undercorrection after an external levator resection operation. I shall also show the results of this and other blepharoptosis operations for this condition when trauma is causative.

A simple classification of the various causes of acquired blepharoptosis is given in Table 2, based on the reports of the investigators cited in Table 1. In 101 consecutive cases of acquired blepharoptosis, trauma (Table 3) was the most common single cause.

## MATERIAL AND METHODS

Surgery was performed on 40 patients with unilateral traumatic blepharoptosis. An internal approach was used in 11 cases and an external approach in 26 in order to retrieve a severed levator muscle or to resect an intact one. A Berke-Motais[6] or a Crawford[7] operation was performed on three eyelids with no levator function, with disappointing results.

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When trauma is causative, other problems often complicate the correction of the blepharoptosis. In the present series, these problems consisted mainly of a gross hypotropia (15 cases), adhesions between the levator muscle and the globe (three cases), or between the upper eyelid and the superior orbital margin (three cases), and there may be other assorted problems resulting from previous unsuccessful attempts to repair the blepharoptosis. Some of these complications could be corrected along with the blepharoptosis, but others were insurmountable.

## BLEPHAROPTOSIS CAUSED BY SURGICAL TRAUMA

In 72% of the patients, blepharoptosis developed after an operation on the orbit, the upper eyelid, the globe, or one of the extraocular muscles.

*After orbitotomy*—A transcranial or a lateral orbitotomy caused blepharoptosis in eight patients, most of whom had a good result from a levator resection operation when the levator function was 6 mm or more (Fig. 1). But when the levator muscle was paralyzed, this operation failed. Consequently, such eyelids had to be suspended from the frontalis muscle with a less satisfactory result (Fig. 2).

*After enucleation*—Eight patients had 2-8 mm of unilateral blepharoptosis and an intact levator muscle after an apparently uncomplicated enucleation. Seven of these had 5-12 mm of true levator function,* and these were adequately corrected by either an internal[8] or by an external[9] levator resection (Fig. 3). In order to prevent final over- or

* *True* levator function occurred when the upper eyelid was elevated only by the levator muscle. The levator function was *false* when adhesions between the levator and the globe caused the eyelid to be elevated by the superior rectus muscle rather than by the levator.

TABLE 1

INCIDENCE OF SURGICALLY TREATED BLEPHAROPTOSIS

| Author | No. Cases | Congenital | Acquired | |
|---|---|---|---|---|
| | | | Traumatic | Nontraumatic |
| Johnson[2] | 108 | 85 (79%) | 9 (8%) | 14 (13%) |
| Hamilton[3] | 41 | 26 (63%) | 6 (15%) | 9 (22%) |
| Beard[4] | 140 | 89 (64%) | 16 (11%) | 35 (25%) |
| Smith[5] | 148 | 99 (67%) | 28 (19%) | 21 (14%) |
| Present series | 672 | 571 (85%) | 40 (6%) | 61 (9%) |
| Total | 1,109 | 870 (78%) | 99 (9%) | 140 (13%) |

undercorrection, each of these seven eyelids was positioned on its prosthesis at operation so as to compensate for a greater postoperative "lift" of the eyelid when the levator function was 8 mm or more than when it was only 5 mm. If a small amount of postoperative over- or undercorrection occurred, these defects could be reduced by ordering a new prosthesis of the proper thickness or by having the cornea of the prosthesis moved upward or downward to compensate for the over or undercorrection. Thus, a pleasing result (Fig. 4) could be achieved without additional surgery.

The eighth patient had 8 mm of blepharoptosis with no levator function after a long section of the optic nerve had been excised during an enucleation for retinoblastoma. Because the levator muscle was paralyzed, a subsequent levator resection failed to reduce the blepharoptosis. In this case, a Crawford[7] operation may have yielded a more acceptable outcome.

*After operation on conjunctiva*—Seven patients developed 2-12 mm of blepharoptosis after a subconjunctival tumor or cyst had been excised from the globe or from the upper eyelid. In each case the levator tissues above the tarsus had been injured; consequently, the levator function measured only 3-6 mm in three cases and 7-12 mm in the other four.

In five of these seven cases, the retracted end of the severed levator muscle was found through a skin approach and then reattached to the tarsus. When last examined an average of 30 months postoperation, four cases were fully or almost fully corrected (Fig. 5). A conjunctival approach was employed

TABLE 2

CLASSIFICATION OF 101 CASES OF ACQUIRED BLEPHAROPTOSIS

| Classification | Total Incidence |
|---|---|
| Trauma | 40% |
| Idiopathic | 23% |
| Blepharochalasis | 9% |
| Progressive external ophthalmoplegia | 9% |
| Tumors of upper eyelid | 8% |
| Horner's syndrome | 5% |
| Systemic disease | 5% |
| Microphthalmos | 2% |

TABLE 3

CLASSIFICATION OF CAUSES OF 40 CASES OF TRAUMATIC BLEPHAROPTOSIS

| Cause | No. Cases |
|---|---|
| Surgical trauma | |
| Orbital Operations | 8 |
| Enucleations | 8 |
| Conjunctival and eyelid operations | 7 |
| Operations on superior oblique muscle | 4 |
| Operations on lateral rectus muscle | 2 |
| Total | 29 (72% |
| Nonsurgical trauma | |
| Toy, stick, sled, football, golf club | 5 |
| Beer bottle, auto accident, fall | 5 |
| Bullet through orbit | 1 |
| Total | 11 (28%) |



Fig. 1 (Berke). Traumatic blepharoptosis caused by enophthalmos after Kronlein operation. Left: Before external levator resection. Right: Three years after operation.

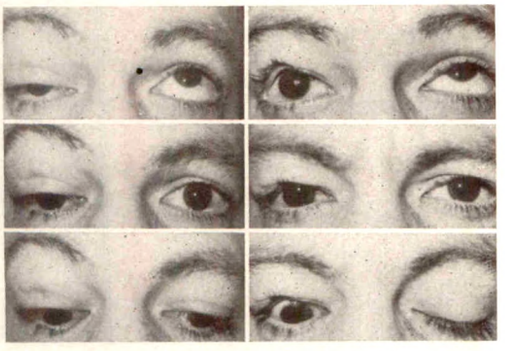


Fig. 2 (Berke). Traumatic blepharoptosis caused by injury to third nerve during Kronlein operation. Left: After a Friedenwald-Guyton and two levator resection operations. Right: Twenty-one months after a Crawford operation.

in two of the seven cases, but the retracted levator tissues could not be found by this technique; consequently, both were found to be much undercorrected months later.

When the external approach was employed to retrieve a severed levator muscle, an intact medial or lateral horn usually lead the surgeon to the retracted end of the muscle. But when both horns had been severed and the levator had receded out of sight into the epibulbar tissues, the lost levator could be found and identified only by grasping and pulling these tissues forward on a blepharoptosis clamp while the surgeon palpated the trochlea for Whitnall's check ligament. If the levator had been caught in the clamp, the surgeon would feel a cord-like band (Whitnall's ligament) extending from the trochlea towards the clamp. By this means the surgeon could find a lost levator and free it from the surrounding tissues without jeopardizing the underlying superior rectus or the superior oblique tendon.

When repairing this kind of blepharoptosis, the surgeon must realize that the postoperative lift of the eyelid will be greater when the levator action is good than when it is poor. In other words, he must position the blepharoptotic eyelid on its cornea at operation so as to fully compensate for this postoperative lift.

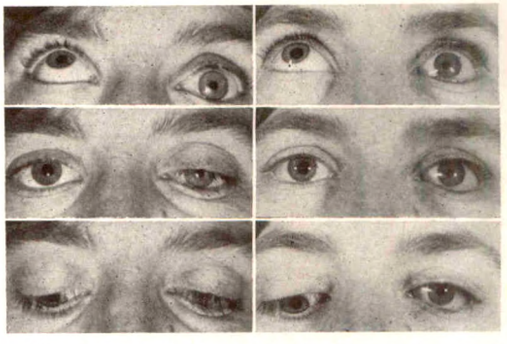


Fig. 3 (Berke). Traumatic blepharoptosis caused by enucleation. Left: Before external levator resection. Right: Eight months after operation.

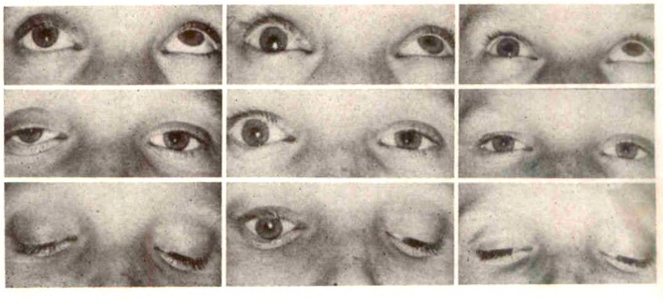


Fig. 4 (Berke). Traumatic blepharoptosis caused by enucleation. Left: Before external levator resection. Center: Three months after operation with preoperative prosthesis in place. Right: Six months after blepharoptosis operation with new prosthesis.

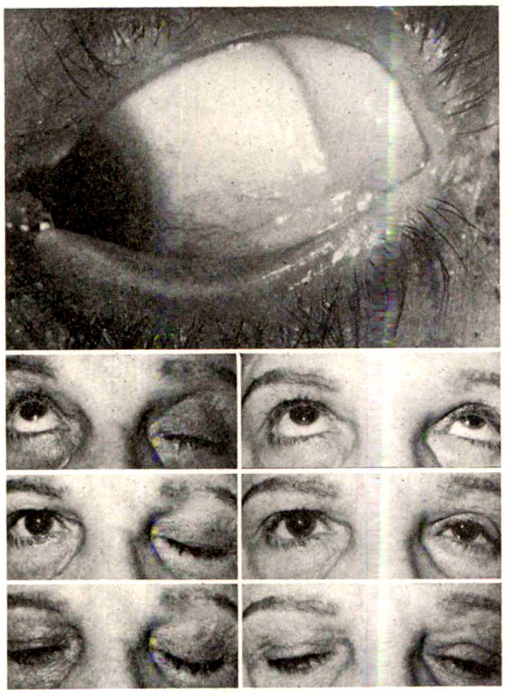


Fig. 5 (Berke). Traumatic blepharoptosis caused by excision of dermolipoma. Top: Position of tumor before excision. Left: Blepharoptosis after excision of tumor. Right: Two months after external levator resection.

*After extraocular muscle operations*—Two patients developed 3-5 mm of blepharoptosis after a strabismus operation had severed the latter horn of the levator aponeurosis. Both blepharoptotic eyelids were corrected by advancing the severed aponeurosis to the upper tarsus by an external (Fig. 6) or by an internal approach (Fig 7).

Four other patients developed an uncompromising type of blepharoptosis after an operation on the superior oblique tendon. In each case, the superior rectus had been severed from the globe in a prolonged and extensive search for the superior oblique tendon. So much excessive manipulation of the epibulbar tissues caused dense postoperative adhesions between the globe and the trochlea, and also between the levator muscle and the superior rectus. Consequently, each patient developed a spurious type of levator function, in which the blepharoptotic eyelid was elevated from downgaze to upgaze more by the superior rectus muscle than by the levator muscle. In such cases, a levator resection operation was most difficult and unpredictable, not only because the adhesions bound the levator to the superior rectus muscle, but also because the adhesions reformed —even when such inert materials as Gelfoam, Gelfilm, silicone rubber, or Supramide Extra had been placed under the levator to prevent their reformation.

Figure 8 illustrates one of the better cosmetic results obtained in one such case after two external levator resections. The blepharoptosis was well corrected, but the patient had to keep her eyelids taped together during

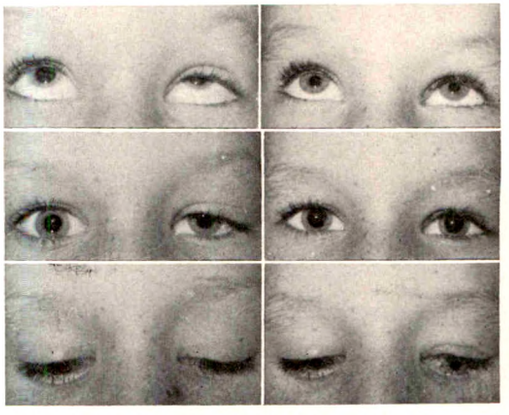


Fig. 6 (Berke). Traumatic blepharoptosis caused by recession of external rectus muscle. Left: Before external levator resection. Right: Six weeks later.



Fig. 7 (Berke). Traumatic blepharoptosis after resection of left external rectus. Left: Before internal levator resection. Right: Three months afterward.

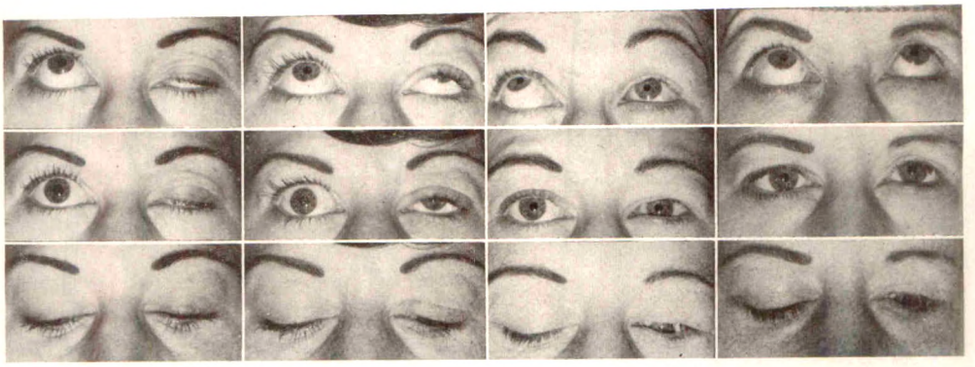


Fig. 8 (Berke). Traumatic blepharoptosis caused by tenotomy operation on left superior oblique. Far left: Three months after Friedenwald-Guyton operation. Center left: Six months after first external levator resection. Center right: Two months after second external levator resection. Far right: Three years after excision of redundant upper lid skin.

sleep for months to prevent postoperative exposure keratitis.

Another patient had blepharoptosis and levator-to-globe adhesions after an operation on the superior oblique tendon. She had a fascia lata frontalis operation with an outcome (Fig. 9) even worse than that shown in Figure 8

### Blepharoptosis caused by nonsurgical trauma

Nonsurgical trauma caused blepharoptosis in 11 patients. Ten experienced upper eyelid trauma, and in one, the blepharoptosis resulted from a self-inflicted bullet wound to the orbit. When these patients were examined months or even years after the initial trauma, the degree of blepharoptosis varied from 2 to 7 mm and the levator function from 3-10 mm.

In nine of the 11 patients the levator tissues had been severed above the tarsus. Some of these had obvious scars *only* on the underside of the lid—an observation completely missed by the examiner at the time of the initial repair. Another patient, whose blepharoptosis occurred after a blunt football injury, had no visible scars whatever on either surface. These observations indicate that we must examine both sides of the upper eyelid when repairing face lacerations.

An external approach was employed in eight of these 11 patients to find the retracted end of the severed levator tissues. After exposing the epibulbar tissues and rotating the globe downward, a thin layer of scar tissue or an intact medial or lateral horn usually guided the surgeon to the retracted end of the severed levator. But when the levator had retracted into the thick epibulbar tissues, it had to be retrieved by pulling the epibulbar tissues forward on a blepharoptosis

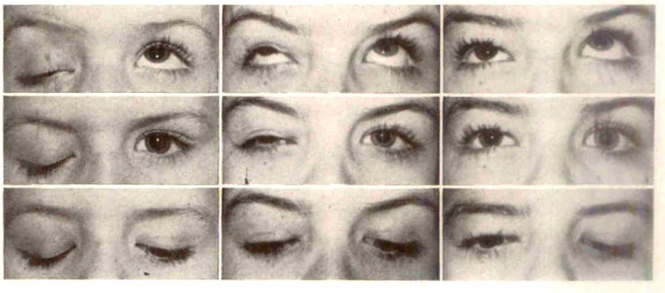


Fig. 9 (Berke). Traumatic blepharoptosis caused by resection of right superior oblique tendon. Left: Before Berke-Motais operation. Center: Before Crawford operation. Right: One year later.

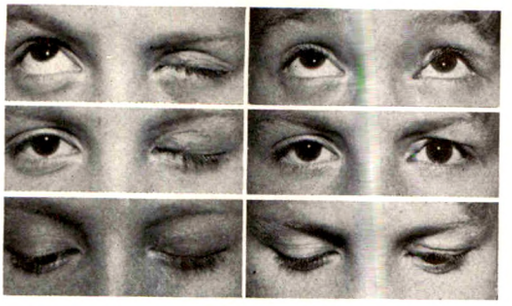


Fig. 10 (Berke). Traumatic blepharoptosis due to eyelid laceration by sled runner. Left: Two months after accident. Right: Six months after external levator resection. Note overcorrection.

clamp as previously described. By this maneuver, the surgeon could find the lost levator and reattach it to the tarsus.

Since the surgeon could rarely identify the exact end of the levator muscle, especially when it was imbedded in the epibulbar tissues, he had to decide whether to shorten the levator and risk final overcorrection (Fig. 10), or to merely advance it to the tarsus and chance getting final undercorrection (Fig. 11). Consequently, two of these nine patients required a subsequent levator resection (including patient shown in Fig. 11), while others needed a levator recession operation before a satisfactory outcome could be achieved. Until reliable guidelines become available, it seems wise to err on the side of overcorrection rather than undercorrection. The most important thing is to find the levator, and then aim for overcorrection, since receding the levator is less difficult than resecting the muscle for undercorrection.

The 11th case was a 53-year-old man who had 6 mm of blepharoptosis after a bullet injury to the right orbit. Examination years later disclosed 7 mm of levator function, a blind right eye, 30 prism diopters of right hypotropia, an atypical von Graefe sign, and corneal anesthesia.

Even after he had been alerted to the danger of postoperative keratitis, this patient was eager to have the blepharoptosis repaired because it was a source of embarrassment to him at his job.

At operation the right inferior rectus was receded for the hypotropia, and the levator was resected for the blepharoptosis. Two weeks later both appeared well corrected, and the cornea was clear. But in the ensuing weeks an intractable neuroparalytic keratitis developed, despite local treatment and intermarginal adhesions. At the patient's suggestion the eye was enucleated three months after the blepharoptosis operation. With a prosthesis in place, the blepharoptosis was fairly well corrected, but the final outcome was unsatisfactory (Fig. 12).

In retrospect, I believe this patient would have had a better result if a thick Gunderson flap had been turned down over the cornea[10] and a thin custom-made cosmetic shell fitted over the flap.

The final results of these 40 operations were appraised from one month (three cases) to 78 months (one case) after operation, the average being 19 months.

## Discussion

An internal approach to the levator yielded a good result only when the levator

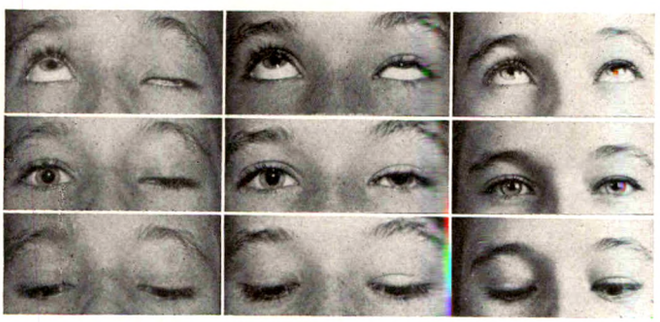


Fig. 11 (Berke). Traumatic blepharoptosis due to subconjunctival laceration of upper eyelid by golfer's putter. Left: After accident. Center: Undercorrection 10 months after external levator resection. Right: Six months after second external resection.



Fig. 12 (Berke). Traumatic blepharoptosis caused by bullet injury to right retrobulbar tissues. Left: Before external levator resection. Center: Corneal ulceration three months later. Right: Six months after enucleation.

function was more than 5 mm from downgaze to upgaze and the levator muscle was intact. An external approach usually gave better results when the levator function was less than 5 mm, or when the levator tissues had been severed above the tarsus. It was the operation of choice when the levator function measured 3 mm or more from downgaze to upgaze. This was so mainly because the external approach gave better exposure of the epibulbar tissues.

Since reliable guidelines for the correction of such cases were unavailable, 20 of the 26 external operations were analyzed to evolve a provisional formula for avoiding gross amounts of postoperative overcorrection and undercorrection by this procedure. Only two of these 20 blepharoptotic eyelids "fell" postoperatively. (An eyelid was said to have fallen when it covered more cornea postoperatively than it did at the end of operation. A postoperative "lift" occurred when the eyelid covered less cornea postoperatively than at the end of operation. Since the other 18 eyelids registered a greater postoperative "lift" when the levator function was good than when it was poor, the proposed guidelines were based on these observations.

These guidelines showed that the surgeon must position the blepharoptotic eyelid at operation so as to compensate for a greater postoperative lift when the preoperative levator function is 8 mm or more than when it is 5 mm or less. For example, if the normal eyelid covered its cornea 2 mm in the primary position (called the target area), and if the levator function indicated a postoperative lift of 4 mm, then the blepharoptotic eyelid should be raised at operation to cover its cornea 5 mm (3 mm below the target area) in order to offset a postoperative lift of 4 mm which would result in 1 mm of overcorrection.

Unfortunately, the 20 cases analyzed failed to provide enough data on which to calculate the amount of lift for each degree

TABLE 4

GUIDELINES FOR CORRECTION OF TRAUMATIC BLEPHAROPTOSIS BY EXTERNAL APPROACH

| Levator Function | Target Area* | Eyelid Position† at Operation | Postoperative Lift of Eyelid | Amount of Overcorrection |
|---|---|---|---|---|
| 3–4 mm | −2 mm | −2 mm | 1 mm | 1 mm |
| 5–6 mm | −2 mm | −3 mm | 2 mm | 1 mm |
| 7–8 mm | −2 mm | −4 mm | 3 mm | 1 mm |
| 9–10 mm | −2 mm | −5 mm | 4 mm | 1 mm |
| 11–12 mm | −2 mm | −6 mm | 5 mm | 1 mm |

* Target area is the position of normal eyelid below the upper limbus in primary position.

† Position of blepharoptotic eyelid below the upper limbus at the end of operation with cornea in primary position.

of levator function. Therefore, the guidelines in Table 4 are based upon extrapolations and can serve only as gross approximations for preventing large amounts of over- or undercorrection when an external approach is used. Table 4 may save the surgeon much guesswork when using an external approach for this type of blepharoptosis. These data are useful only when the levator and the orbicularis muscles are relaxed under deep surgical anesthesia. Moreover, they are designed to give over- rather than undercorrection for the reasons already mentioned.

## Summary

The surgical results in 40 patients with traumatic blepharoptosis were examined to ascertain which type of operation gave the best results. An external (skin) approach gave better exposure and yielded better results than an internal (conjunctival) approach for retrieving a retracted levator severed in the eyelid. These operations, however, were useless when the levator muscle was paralyzed. In such cases the blepharoptotic eyelid had to be suspended from the frontalis or from the superior rectus muscle with, however, a less satisfactory outcome.

A Crawford fascia lata operation is indicated for patients with unilateral traumatic blepharoptosis only when the levator muscle is paralyzed. The external approach is the procedure of choice for retrieving a severed levator muscle when the levator function is 3 mm or more from downgaze to upgaze. Gross amounts of over- or undercorrection can be avoided by this approach only when the surgeon positions the blepharoptotic eyelid on its cornea at operation so as to compensate for a greater postoperative lift of the eyelid when the levator function is good than when it is poor.

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# EXOPHTHALMOS AND POSTERIOR FRONTOCELE WITH FIBROUS WALL ON ORBITAL SIDE

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Frontocele with exophthalmos is usually of the anterior type where there are the following characteristic signs: (1) The globe is pushed down and out. (2) There is a palpable mass below the upper, inner orbital margin. (3) In gigantic frontocele, there may be a bulging of the forehead.[1] (4) The diagnosis can be made clinically without difficulty by an otolaryngologist, especially by transillumination. (5) Characteristic changes are seen on x-ray examination of the skull: There is bone condensation around the mucocele,[2] affection of the superior orbital margin accompanied by opacity of the affected frontal sinus, and there may be a fluid level. There is usually a widening of the orbital cavity in very large frontoceles. Skull x-ray films after Lipidol injection of the affected sinus are impressive.

Exophthalmos that results from an early posteriorly placed fronocele usually does not show any of these characteristic signs when it is surrounded on the orbital side by fibrous tissue (the bone having been absorbed). In skull x-ray films, the absorbed bone is overshadowed by the surrounding orbital bones. A small palpable mass deep in the upper or upper-inner part of the orbit that is found to be pushing the globe slightly downward is not diagnostic.

Two cases of posteriorly placed frontocele with exophthalmos were found among 50 cases of radiographically and surgically proven frontoceles with exophthalmos. These are described here because the condition is very rare. If the mucocele is deep, not palpable externally, the proptosis is usually diagnosed as of uncertain etiology, and such cases may not receive proper treatment. The two cases described herein were not correctly diagnosed until orbital exploration.

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## EXAMINATION AND FINDINGS

The first patient (Case 1) was a 40-year-old man with right proptosis, 21 mm in degree, of three years' duration (Fig. 1). The second patient was a 35-year-old woman whose proptosis was on the left side, 20 mm in degree, and was of four years' duration (Fig. 2).

In both cases, proptosis was unilateral and had progressed gradually over several years. There was no important family history and no history of trauma or past x-ray therapy. Neither patient showed signs of endocrine dysfunction, and there was no enlargement of the thyroid, liver, or spleen. Chest and abdominal examinations revealed no abnormality. There were no cafe-au-lait areas of



Fig. 1 (Mortada). Case 1. Right proptosis of three years' duration due to a surgically proved posterior frontocele.

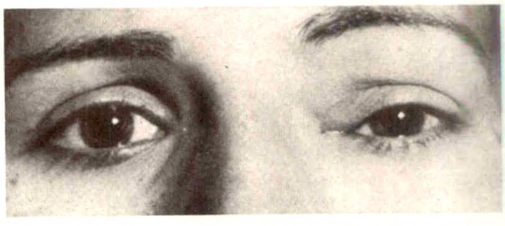


Fig. 2 (Mortada). Case 2. Left proptosis of four years' duration due to a surgically proved posterior frontocele.

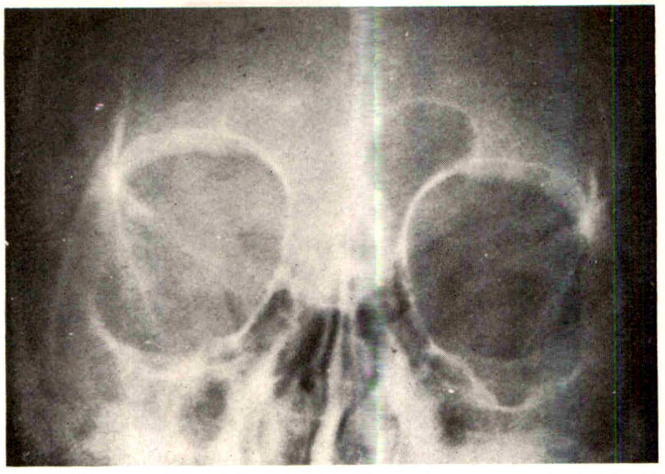


Fig. 3 (Mortada). Case 1. Postero-anterior skull x-ray taken with 20° tube tilt showing intact right superior orbital margin. The right frontal sinus is opaque, and the opacity is continuous with upper part of nasal cavity. There is no radiologic evidence for right orbital frontocele. The left frontal sinus is clear.

skin pigmentation, no nodules, no hemangiomas, no tumors.

Temperatures, pulse, blood pressure, urine, feces, blood total and differential counts, bleeding and clotting times were within normal limits. Tuberculin tests, the Wasserman, and the Casoni test for hydatid cyst all proved negative. Basal metabolic rate and $^{131}I$ uptake were within normal limits. All roentgenogram studies except those of the skull revealed bone structure to be normal.

The proptosis was neither intermittent nor pulsating, and neither case showed signs of an acute inflammatory process. In the first case, there was no palpable orbital mass; in the second, a small mass was palpable deep in the pper medial part of the orbit. In both patients, the unaffected eye was normal. In each, there was upward limitation of ocular movement, but the fundi and visual acuity (6/9) were not affected. Examination showed only an opaque frontal sinus on the affected side in each case.

Additional skull roentegographic studies were undertaken as follows to further examine the orbital bones and surrounding sinuses: occipital views for the frontal and maxillary sinuses; postero-anterior views (taken at a tilt of 20°) for frontal, maxillary, and anterior ethmoidal sinuses and nasal septum; two oblique views for posterior ethmoidal sinuses and optic canals; lateral views for the frontal, maxillary, and sphenoid sinuses; and views of the base of the skull for the ethmoid and sphenoid sinuses.

## Results

In the first case, the postero-anterior x-ray view of the skull shows an intact right superior orbital margin (Fig. 3). The right frontal sinus is opaque, and the opacity is continuous with the upper part of the nasal cavity. There is no definite radiologic evidence for a right orbital frontocele. The left frontal sinus is clear.

In the second case, the postero-anterior x-ray view of the skull shows an intact left superior orbital margin (Fig. 4). The left frontal sinus is opaque, but there is, again, no definite evidence for a left orbital frontocele. A dense linear sclerosed bone condensation is present in the middle of the left frontal sinus, perhaps representing the upper side of the mucocele.

*Surgical exploration*—In both cases, orbital exploration revealed a cyst of approximately 2 × 2 cm in the upper medial part of the orbit continuous with the frontal sinus. Each cyst contained a dark green, thick mucoid fluid with a few degenerated polymorphonuclear cells and no hairs. Histopathologically, these cysts were composed of fibrous tissue with mononuclear infiltration. The

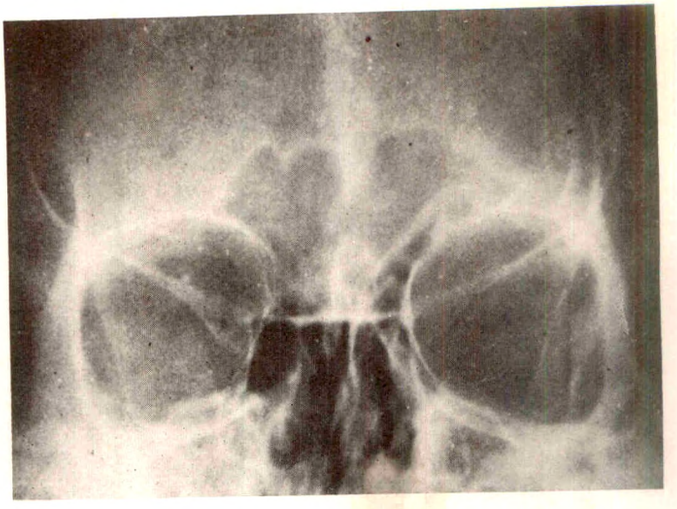


Fig. 4 (Mortada). Case 2. Postero-anterior skull x-ray taken with 20° tube tilt showing intact left superior orbital margin. The left frontal sinus is opaque. There is no definite radiologic evidence for left orbital frontocele. A dense linear sclerosed bone condensation is present in the middle of the left frontal sinus, perhaps representing the upper side of the mucocele.

walls were lined in some areas by columnar epithelium. There was no skin lining, no sebaceous glands, nor hair follicles. The diagnosis in each case was frontocele.

## Comment

The two frontal sinuses vary in size in different individuals. Occasionally, they extend backward into the roof of the orbital cavity as far as the optic foraminae. The potential extent of a frontal mucocele depends on the original size, extent, and pneumatization of the affected sinus. All or part of the sinus may be affected, and the size of the mucocele also depends upon the density of the boney wall of the sinus and how it reacts to the presence of infection and to the degree of pressure created by the fluid within the mucocele. The expanding mucocele may thus produce pressure atrophy, thinning, or sclerosis of the bony wall of the sinus,[3] with corresponding variations in the radiographic picture.

In an earlier paper,[4] I described 30 cases of frontocele with exophthalmos and classified these according to the status of the superior orbital margin as seen on skull roentgenograms. In cases in which the superior orbital margin is affected, there may be (1) complete affection by absorption, or by sclerosis and depression, or there may be (2) partial affection by depression. The depressed area may be thin and not visualized, it may be sclerosed, or it may be unchanged in density. The affected area may involve the inner one-third, the middle third, or the medial half of the margin. Mucoceles affecting only a part of the superior orbital margin are usually seen in a younger age group than those affecting the complete margin.[5]

In cases in which the superior orbital margin is not affected, this is due to the fact that the frontocele extends posteriorly. In such cases (1) the mucocele may be evident on skull roentgenograms, being surrounded by bone condensation, or (2) it may not be visualized, being surrounded by thinned or absorbed bone and thus overshadowed by the surrounding orbital bones. This was the case in the two patients described in this paper. If the mucocele is deep and there is no externally palpable mass, as in the first of the two cases presented herein, it is impossible to demonstrate clinically the cause of the proptosis.[6]

## Summary

In two patients with slowly increasing proptosis, posterior orbital frontocele proved to be causative on surgical exploration, but this cause could not be demonstrated preoperatively. In each case, the lesion was surrounded on the orbital side by fibrous tissue,

the bone having been absorbed, and thus these frontoceles could not be visualized on skull x-ray examination because they were overshadowed by the surrounding orbital bones. Since these cysts are deep and may not be palpable externally, as in the first of these two cases, the proptosis may be diagnosed as of uncertain etiology and proper treatment may not be instituted. Only orbital exploration, with histopathologic examination of the wall of the mucocele and the fluid it contains, are diagnostic.

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## Ophthalmic miniature

"A devil of a man," said Robert Poussepain. "He shows himself; he's a hunchback. He walks; he's bowlegged. He looks at you; and he has only one eye. You speak to him; but he is deaf. Why, what does this Polyphemus do with his tongue?"

"He speaks when he wishes," said the old woman. "The ringing of the bells has made him deaf. But he's not dumb."

"So that is lacking to him?" observed Jehan.

"And he has one eye too many," added Robert Poussepain.

"Not so," said Jean judiciously. "A one-eyed man is much more incomplete than a blind man, for he knows what it is that's lacking."

Victor Hugo

*The Hunchback of Notre Dame*

# NEW APPROACH TO THE TREATMENT OF SELECTED RETINAL DETACHMENTS SECONDARY TO VITREOUS LOSS AT CATARACT SURGERY

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A typical retinal detachment may develop in some aphakic patients as a result of massive vitreous incarceration in the cataract wound. The lower half of the retina is elevated, often including the nonpigmented epithelium of the pars plana, and there may be inferior breaks. Vitreous extends from its attached base below to the cataract wound above (Fig. 1). This sheet of vitreous apparently shrinks gradually pulling the inferior retina into the pupillary area. The extent of the retinal detachment is determined by the location of associated retinal breaks.

When a single strand of vitreous extends up to the wound, this has sometimes been cut and a conventional buckling procedure successfully carried out, but a large sheet of vitreous pulling the retina to the wound above presents a much more difficult problem.[1,2] In the past, we have not attempted to cut the vitreous free from the wound. Rather, we have utilized a high segmental or encircling buckle to attempt to establish contact between the choroid and retina. In some successful cases the buckle has been high enough to obstruct the function of the posterior polar area.

With the introduction of an instrument to cut and remove vitreous, in situ, via the pars plana—the vitreous infusion suction cutter (VISC)[3]—it became apparent that a new approach to this type of complicated detachment would be to cut and remove the vitreous from the anterior segment. Vitreous traction is immediately relaxed and the retina falls back towards its normal position. A conventional buckling procedure may then be carried out.

This paper presents the results of this surgical technique in four eyes. A single case is reported in greater detail to better illustrate the problem and this method of its management.

## CASE REPORT

*Case* 1—A cataract extraction performed August 2, 1965, on the left eye of this patient was complicated by extensive vitreous loss and iris incarceration in the wound. On August 9, a disrupted wound was repaired. The patient was first seen at the Bascom Palmer Eye Institute on December 23, 1965. Best visual acuity was 20/25 in the right eye, 20/40 in the left. The inferior retina and the thin ciliary epithelium was elevated by a dense vitreous condensation extending from the vitreous base be-

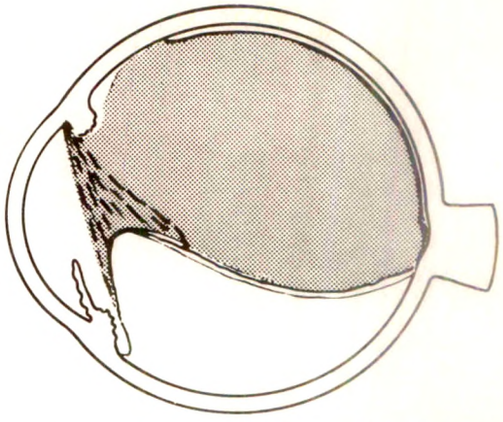


Fig. 1 (Norton and Machemer). Schematic drawing of an eye with vitreous incarceration into the cataract wound and secondary retinal detachment.

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low to the cataract wound above. The ciliary epithelium was so thin that initially it was misinterpreted as a dialysis extending from three to 8:30 o'clock.

On December 27, a scleral buckling procedure was performed. Since it seemed impossible to reattach the retina and ciliary epithelium anterior to the equator, it was decided to place a buckle so that the retina would be attached in the region of the equator or slightly posterior to it. Therefore, a scleral undermining was done inferiorly from 2:30 to 10 o'clock. Diathermy applications and a silicone plate were placed in the undermined bed and a 360-degree band was used. Postoperatively, the retina was attached on and posterior to the buckle. Anteriorly, however, the retina remained elevated in the inferior half where there was extensive traction by the vitreous. On January 14, 1966, because of increasing elevation of the retina anterior to the buckle, photocoagulation was placed to the crest of the buckle. On January 31, it was evident that the detachment had extended across the buckle and the lower half was detached. The macula was still attached with a visual function of 20/70. No further surgery was planned, since it appeared impossible to release the vitreous traction.

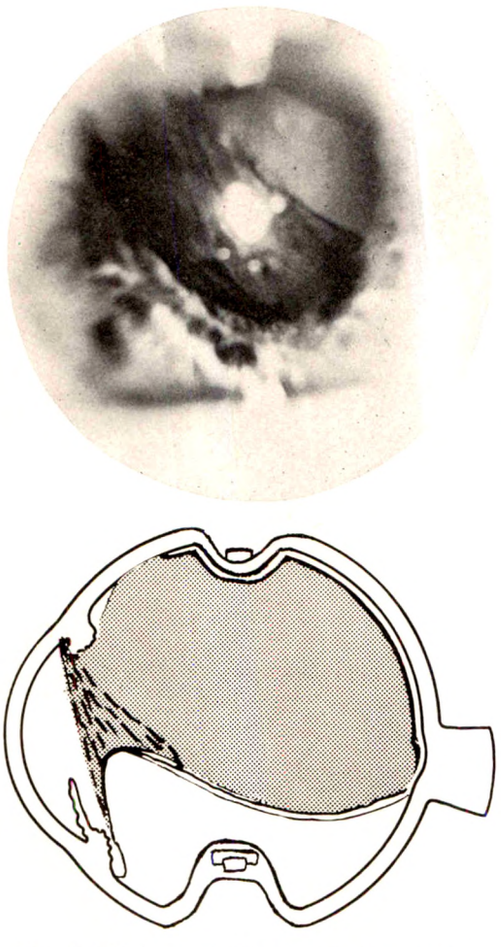


Fig. 2 (Norton and Machemer). Case 1. Top: Preoperative photograph. Vitreous is incarcerated in the cataract wound and pulls on the inferior pars plana and retina. Pars plana epithelium is visible in the pupillary area on retrograde illumination. Bottom: Schematic drawing of same eye showing encircling buckle from which the retina became loose because of further shrinkage of incarcerated vitreous.

During the subsequent four and one-half years, the patient was followed and noted to have a gradual increase in the elevation of the inferior retina with further shrinking of the vitreous membrane. Associated with this, visual function dropped to counting fingers at four feet. At this point it should be noted that the retinal ciliary epithelium was drawn up so that it was visible in the pupil (Fig. 2).

On October 19, 1970, the vitreous infusion suction cutter was introduced into the eye via the pars plana temporally. The vitreous membrane was cut out of the anterior chamber along with a moderate amount of the vitreous occupying the posterior chamber. This resulted in a prompt mobility and flattening of the detached retina and ciliary epithelium. The previously placed buckle was revised and retreated with cryotherapy without shortening the encircling element. Air was injected into the vitreous cavity. Except for a small fold in the macular region, the retina has remained attached postoperatively (Fig. 3). Best visual acuity is 15/400.

## Clinical experience

Four cases were treated in the manner outlined above. Beside the patient whose case is reported, one other had also had a previous unsuccessful primary buckling procedure. In both of these cases, failure resulted from the inability to produce firm chorioretinal adhesions because of the immobility of the highly elevated retina and progressive vitreous shrinkage. Following removal of vitreous, the retina became mobile and was reattached with an encircling buckle.

In the other two cases, vitreous surgery was undertaken as the primary procedure. In one, the retina became so mobile an attempt was made to reattach it by intraocular air tamponade[4] and cryotherapy, without a buckling element. The retina became detached again within three weeks from a small superotemporal dialysis even though it had been recognized and treated at the time of the original surgery. Reoperation with a

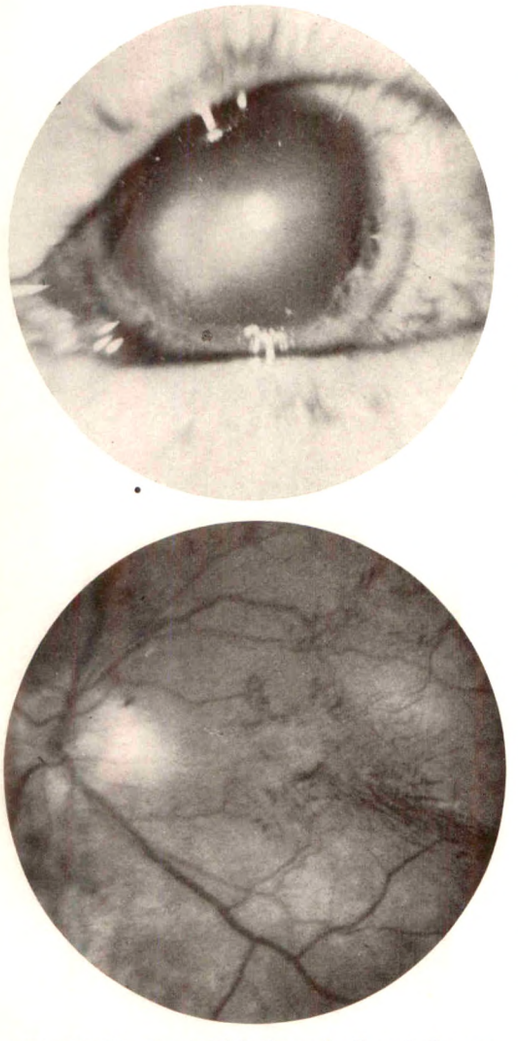


Fig. 3 (Norton and Machemer). Case 1. Postoperative photograph. Top: Retrograde illumination shows a red reflex from the pupil after vitrectomy. Bottom: Fundus photograph with retina attached.

360-degree buckle resulted in retinal reattachment. Because of this experience. the fourth case was treated initially by vitrectomy combined with a 360-degree buckle and cryotherapy. This resulted in immediate reattachment.

## Summary

Vitreous removal, utilizing the vitreous infusion suction cutter, combined with a scleral buckling procedure, was the method of management in four cases of retinal detachment associated with extensive vitreous incarceration in the cataract wound. Two of these patients had undergone previously unsuccessful primary buckling procedures. Failure in these two cases was due to the presence of extremely elevated and immobile retina and progressive vitreous shrinkage. This combination of circumstances prevented the achievement of firm chorioretinal adhesions. In the other two cases, vitreous surgery was undertaken as the primary procedure. Successful re-attachment was achieved in all four patients.

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# TROPICAL AMBLYOPIA IN NIGERIANS

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The syndrome of tropical nutritional neuropathy has been described in many parts of the tropics and in prisoners-of-war camps.[1–5] It is frequently referred to as tropical ataxic neuropathy because of the marked sensory ataxia demonstrated by patients with this syndrome. In parts of Nigeria, the prevalence of the disease among adults is as high as 14-26 per 1000.[6–8] It is a major cause of blindness in Nigeria, as amblyopia is usually a feature, and often the presenting sign of the disease. In 1952, Degazon[9] labeled the ophthalmologic deficit tropical amblyopia, a term indicating that the condition is predominantly a disorder of warm countries. Recently, a causal relationship was demonstrated between chronic cyanide intoxication of dietary origin and tropical nutritional neuropathy.[5,7,10]

In this paper, the ophthalmic findings in 360 Nigerians with this syndrome are reported in detail.

## MATERIAL AND METHODS

The subjects of this study are 360 Nigerian patients with tropical nutritional neuropathy, more often referred to as tropical ataxic neuropathy because of the marked sensory ataxia in these patients. In Nigerians, the syndrome is comprised of bilateral optic atrophy and sensorineural deafness, panmyelopathy, and peripheral neuropathy. The diagnosis is usually made when any two of these four components are present.[5] Of these patients, 132 were investigated in University College Hospital (UCH); the rest were seen and investigated during neurologic surveys of two villages, Epe and Ososa, situated in Southern Nigeria, an endemic focus of the disease.

Detailed clinical evaluation, and full neurologic and otologic assessment (including tuning fork tests, audiometry, and determination of threshold drift) were carried out.

Biochemical investigations were directed towards determining the nutritional status with regard to protein-calorie deficiency, mineral and vitamin nutrition, assessment of renal and hepatic function, and exclusion of diabetes mellitus. In order to assess chronic cyanide intoxication concentrations of cyanide and thiocyanate (the major detoxification product of cyanide) in the plasma, and thiocyanate in 24-hour urine, and serum $B_{12}$ levels were estimated as previously described.[5,11]

Cerebrospinal fluid was examined in hospitalized patients, and in a number of these patients, anterior tibial nerve biopsies were done and subjected to histologic examination, single nerve fiber preparation, and electron microscopy. Also, many patients were studied with electrocardiography, electromyography, and by determination of motor nerve conduction velocity. Urine was examined for albuminuria, porphobilinogen, and schistosoma ova. Estimation of plasma protein-bound iodine, $^{125}I$ tri-iodothyronine red blood cell uptake, Kay's augmented histamine test meal, tests to exclude malabsorption, examination of blood films stained to show malaria parasites, and serologic tests for syphilis (Kahn's test and Venereal Diseases Laboratory Research slide tests) were also done.

*Ophthalmic investigations*—Tests of visual acuity were carried out (Snellen). Central and peripheral visual fields were examined by the confrontation method. During field surveys, scotomas were easily demonstrated, when present, by confrontation, using 5 mm white and red test objects. Perimetry and examination by a 2 meter Bjerrum

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screen (using white test objects of 2, 5, and 10 mm) were done in a third of the patients, mostly those who were hospitalized. Refraction was also carried out in the hospitalized group.

## Findings

In parts of Southern Nigeria where cassava forms the staple diet, there are well known foci where the disease is endemic, with males and females affected equally. The highest incidence is in the fourth and fifth decade (Table 1). All the patients gave a history of poor diet in which the staple food was cassava, eaten usually three times a day. Cassava (Mannihot) contains a cyanogenetic glycoside, linamarin, from which hydrocyanic acid is released on enzymatic or acid hydrolysis. The patients belonged to the poorer socioeconomic classes. In 41% of the patients, there was a history of another family member similarly affected. In 50% of familial cases, husbands and wives were affected. In 30 of the patients, a history was obtained of preceding febrile illness occurring one to eight weeks before the onset of symptoms. In 18 female patients, the illness began during the last two trimesters of pregnancy. In 13 other females, onset of symptoms coincided with lactation. Smoking of tobacco and drinking of alcoholic beverages were uncommon habits, occurring in moderation in about 10%, as these patients were poor.

Usually, patients presented at the hospital long after onset of their disease. None presented within four months of onset of symptoms. They finally sought treatment because of increasing ataxia of gait, weakness of legs, or worsening vision; 65% had had symptoms for more than three years before seeking medical care.

As far as ataxia and weakness were concerned, mode of onset was usually gradual. Impairment of vision, however, was sometimes sudden. A history of intermittency in severity of symptoms was obtained in 8%, with symptoms such as paresthesia being worse during the rainy season, pregnancy, lactation and febrile episodes. Two patients described complete remissions; this was confirmed in one, who was seen during remission. In the rest of the patients, the illness was progressive initially, subsequently becoming static.

TABLE 1

AGE AND SEX DISTRIBUTION IN 360 NIGERIAN PATIENTS WITH TROPICAL ATAXIC NEUROPATHY

| Age in Years | Males | Females | Total |
|---|---|---|---|
| 0–9 | 0 | 4 | 4 |
| 10–19 | 11 | 13 | 24 |
| 20–29 | 18 | 28 | 46 |
| 30–39 | 34 | 54 | 88 |
| 40–49 | 43 | 49 | 92 |
| 50–59 | 48 | 21 | 69 |
| 60–69 | 26 | 8 | 34 |
| 70 and over | 2 | 1 | 3 |
| Total | 182 | 178 | 360 |

The most common symptoms encountered in this study were various forms of paresthesia or dysesthesia, usually confined initially to the lower limbs (87%); impaired vision or blindness (80%); ataxic gait (50%); tinnitus and impaired hearing (45%); and weakness in lower limbs (33%). A third of the patients complained of recurrent stomatoglossitis.

Neurologic examination showed posterior column sensory loss (perception of vibration, joint position sense, and two-point discimination), usually in lower limbs. This was associated with sensory ataxia in 80%, and with bilateral perceptive deafness in 40%. It was associated with weakness and wasting of the distal musculature of the lower limbs, and occasionlly of the upper limbs, with glove and stocking sensory loss of superficial sensations (touch, pain, and temperation) in 25% of the patients. Tendon reflexes were commonly absent; they were exaggerated, however, in a few patients in whom hypertonia was present. Occasionally, signs of cerebellar degeneration and disease of the basal ganglia were present. Details of

the clinical picture have been presented elsewhere.[5,7]

In 80 per cent of the patients, ophthalmologic examination showed abnormalities.

*Ophthalmic symptoms*—Early visual symptoms consisted of blurring of vision and loss of details at a distance; familiar faces were not recognizable unless they were very near, and students complained of inability to see the writing on the blackboard. Four patients complained especially of night blindness. In 18 patients all under 30 years of age, blurring of vision was the initial symptom, antedating other symptoms by intervals varying from one month to five years.

Although impairment of vision was usually gradual, a history of sudden onset of blurring of vision was obtained in six patients, five females and one male, all under 30 years of age. In four of them, sudden onset of blurring of vision was preceded by paresthesia in the lower limbs for periods of one, three, four, and seven years. In two other patients, sudden visual impairment occurred early in the morning and was followed by paresthesia in lower limbs one and three months later, respectively. In three of these six patients, transient diplopia and vertigo accompanied the sudden onset of blurred vision, but they were not seen by us during the acute stage. All the patients subsequently developed other symptoms of the disease such as tinnitus and deafness. Only one of these patients was seen before several years had elapsed, and presumably they had episodes of retrobulbar neuritis. The only patient who was seen a week after the sudden onset of blurring of vision was a girl, aged 16 years. She showed evidence of retrobulbar neuritis, with pain in the eyes that was made worse by movement of the eyeballs, severe impairment of visual acuity (less than 6/60 in each eye), slightly dilated pupils with sluggish light reflex, large bilateral paracentral scotomas (easily demonstrable on confrontation and further confirmed by examination on a Bjerrum screen), and pink suffused optic disks with slightly blurred margins on ophthalmoscopy. There was no other neurologic deficit. Six months after onset of visual symptoms, examination of her fundi showed bilateral optic atrophy. In addition, there was evidence of severe bilateral nerve deafness, myelopathy with predominant involvement of the posterior columns, and motor polyneuropathy.

*Ocular findings*—Loss of visual acuity was symmetrical in all but six patients. Among those whose loss was the same bilaterally, nine patients (2.5%) were virtually blind with almost no perception of light. In 130 (36%), visual acuity in both eyes was less than 6/60 and vision was reduced to counting fingers at 18 inches. In 82 patients visual acuity in both eyes was 6/36, and another 58 it was 6/18. In six patients, loss of visual acuity was 6/18 in one eye and 6/60 in the other (with ophthalmoscopic evidence of retrobulbar neuritis in one eye and early optic atrophy in the other). In the patients who were virtually blind and in those with pale white disks, the pupils were large and did not react to light stimulus.

Marked bilateral temporal pallor of the optic disk (Fig. 1) was found in 148 (41.1%). In 22 of these patients, there was

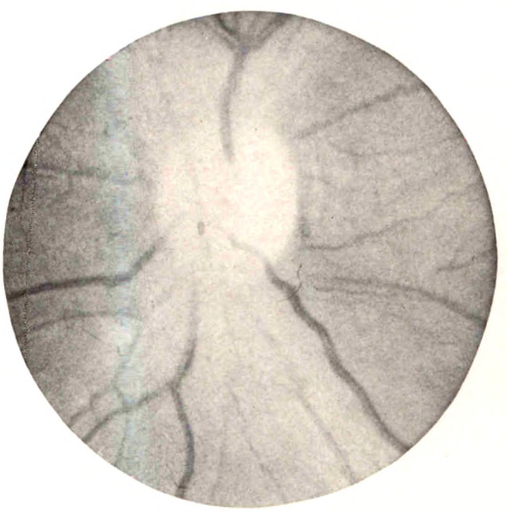


Fig. 1 (Osuntokun and Osuntokun). Temporal pallor (early optic atrophy) in tropical amblyopia in Nigerians.

no history of visual symptoms, but reduction in visual acuity was present. In six patients who had had visual symptoms, bilateral temporal pallor of the optic disk was present, but visual acuity was normal. In the advanced cases the disks were pale white, and atrophic or small, with clear well-defined margins; the retinal arteries appeared attenuated (Fig. 2). This advanced optic atrophy was found in 147 (41%) of patients. Widespread choroidoretinitis with diffuse punctate or patchy pigmentation was observed in both fundi in 12 (3.3%) patients. In 14 (3.8%) patients who complained of blurring of vision, and who showed demonstrable loss in visual acuity, the fundi were surprisingly normal.

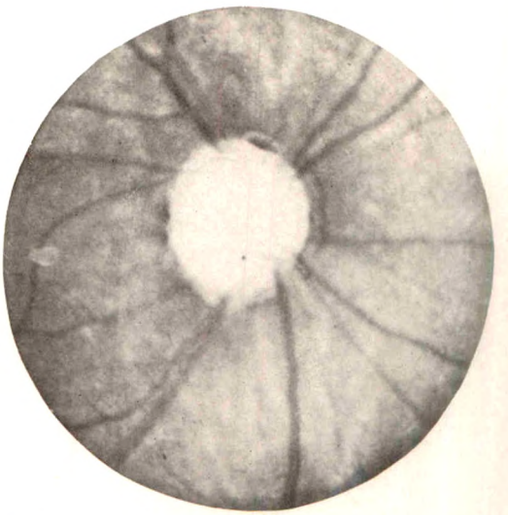


Fig. 2 (Osuntokun and Osuntokun). Advanced optic atrophy in tropical amblyopia in Nigerians.

Concentric diminution of the visual fields (Fig. 3) was the commonest finding and was present in 99 (84%) of the 118 patients in whom the visual fields were examined by perimetry. This presumably progressed to tubular vision (Fig. 4). Central or paracentral scotomas were found in only 16 patients.

*Other findings*—The results of the biochemical, electrophysiologic, and histologic investigations have been presented in detail elsewhere.[5,7,12,13]

There was no biochemical evidence of protein-calorie deficiency. Apart from diminished urinary excretion of riboflavin, the biochemical evidence available suggests that the intake of thiamine, nicotinic acid, and folic acid was adequate.

Cerebrospinal fluid showed no abnormality. Histologic examination of peripheral nerves showed segmental demyelination. Reduced motor nerve conduction velocity was found even in patients who had no clinical evidence of polyneuropathy.

There was biochemical evidence of increased exposure to cyanide in the patients.

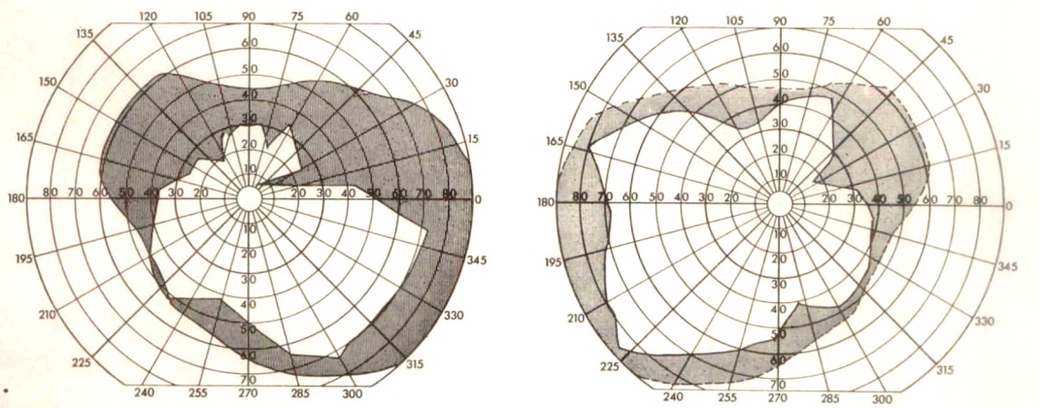


Fig. 3 (Osuntokun and Osuntokun). Example of constriction of peripheral visual fields in tropical amblyopia in Nigerians. Left: Right eye. Visual acuity 6/9. Right: Left eye of same patient. Visual acuity 6/18.

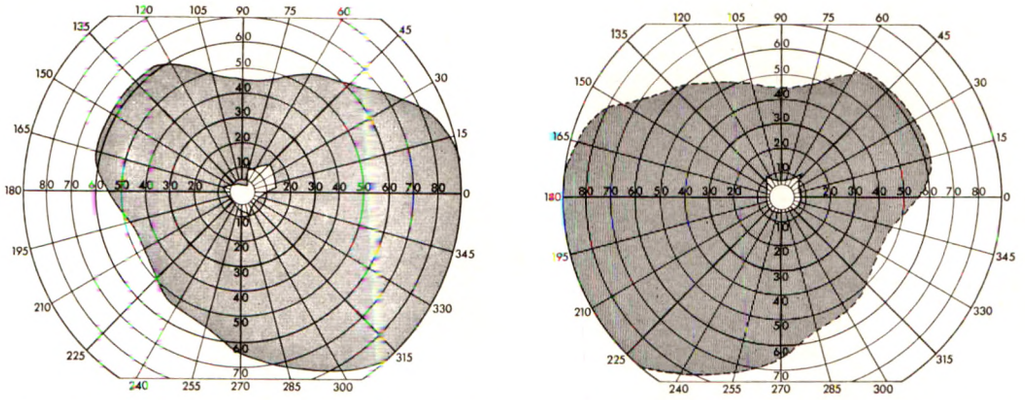


Fig. 4 (Osuntokun and Osuntokun). Example of tubular field in tropical amblyopia in Nigerians. Left: Right eye. Visual acuity 6/60. Right: Leyt eye of same patient. Visual acuity 6/60.

The plasma thiocyanate, cyanide, and urinary excretion of thiocyanate were raised (Table 2). These levels fell (Table 3) and this was accompanied by clinical or symptomatic improvement when patients were fed a hospital diet which contained cassava meals only twice a week. The levels rose again when the patients returned to a cassava diet (Table 4).

There were qualitative changes in the serum $B_{12}$ components which suggested increased exposure to cyanide,[5,7,8] for vitamin

TABLE 2

COMPARISON OF PLASMA AND URINARY DETERMINATIONS IN NORMAL CONTROLS AND IN NIGERIAN PATIENTS WITH TROPICAL AMBLYOPIA*

| | Urinary Thiocyanate† | Plasma Thiocyanate‡ | Plasma Cyanide‡ |
|---|---|---|---|
| Patients with tropical amblyopia | 2.4+0.1 (n=67) | 11.3+0.2 (n=320) | 0.1 +0.004 (n=108) |
| Normal Nigerians | 0.6+0.05 (n=40) | 2.9+0.02 (n=106) | 0.03+0.002 (n=106) |
| | P<0.001 | P<0.001 | P<0.001 |

* Determinations made within 48 hours of admission.

† In micromoles/kg/24 hours (mean plus standard error).

‡ In micromoles/100 ml (mean plus standard error).

TABLE 3

FALL IN PLASMA THIOCYANATE AND CYANIDE AND URINARY THIOCYANATE IN 67 PATIENTS WITH TROPICAL AMBLYOPIA AFTER SIX WEEKS ON HOSPITAL DIET*

| | On Admission | After Six Weeks of Hospital Diet |
|---|---|---|
| Plasma thiocyanate*† | 11.1+0.4 | 2.8 +0.1 |
| Plasma cyanide*† | 0.09+0.004 | 0.03+0.001 |
| Urinary thiocyanate*‡ | 2.4+0.1 | 0.7+0.03 |

* The differences between the concentration on admission and after six weeks on hospital diet are statistically significant ($p<0.001$ for each variant).

† In micromoles/100 ml (mean plus standard error).

‡ In micromoles/kg/24 hours (mean plus standard error).

$B_{12}$ is involved in the detoxication of cyanide.[14-23] The concentration of serum hydroxocobalamin (which probably adsorbs cyanide, and is thereby converted to cyanocobalamin) was reduced in patients. The concentration of cyanocobalamin was raised.

In the plasma of patients, there was an absence or a reduced level of the sulphur-containing amino acids (cysteine, cystein, and methionine)[12]—these are the main donors of thiol groups which combine with cyanide to form thiocyanate, and cystine itself reacts spontaneously with cyanide.[24-28]

TABLE 4

PLASMA THIOCYANATE AND CYANIDE IN 35 PATIENTS WITH TROPICAL AMBLYOPIA ON ADMISSION, SIX WEEKS AFTER ADMISSION (ON HOSPITAL DIET), AND 12 WEEKS AFTER DISCHARGE AND REVERSION TO CASSAVA MEALS

| | Plasma Thiocyanate* | Plasma Cyanide* |
|---|---|---|
| Within 48 hours of admission | 11.9+0.8 | 0.1 +0.006 |
| Six weeks hospitalization and on hospital diet | 2.8+0.3† | 0.025+0.002† |
| Twelve weeks after discharge and return to cassava meals | 12.8+0.9 | 0.11 +0.07 |

* In micromoles/100 ml (mean plus standard error).

† The difference between this figure and the one above it and below it is significant at the $p < 0.0001$ levej. The differences between determinations made upon admission and six weeks after discharge are not significant.

Concentrations of serum calcium, phosphate, sodium, chloride, bicarbonate, and potassium and tests of throid, liver, and renal function were normal. Amino acids and porphobilinogen were absent in the urine. Occasionally schistosoma ova were found in urine of young people. There was no malabsorption. Glucose tolerance tests were not significantly abnormal. Histamine-fast achlorhydria was rare.

Serologic tests for syphilis, typhoid, and typhus gave usually normal results. There was no increased prevalence of infections with malaria in patients.

Electrocardiographic examination usually showed normal results, although sinus tachycardia and nonspecific T-wave changes were occasionally encountered.

## DISCUSSION

The ophthalmic findings in Nigerian tropical ataxic neuropathy are interesting in that the commonest visual field loss was peripheral constriction, although this was often asymmetrical and bizarre. Paracentral and central scotomas were less frequently demonstrable. However, undoubtedly classical retrobulbar neuritis can occur in the Nigerian tropical ataxic neuropathy. In such cases, constriction of peripheral visual fields is not found but paracentral scotoma is easily demonstrable. It is speculative to suggest that the high frequency of contriction of peripheral visual field is due to a higher susceptibility to damage (by a diffusible toxin such as cyanide) of the peripheral receptors in the retina, which are unprotected by an overlying layer of nerve fibers. It has been suggested that cyanocobalamin may act as a "Trojan horse" in the visual system, as cyanide released from this compound by photolysis or electromagnetic waves in the visual spectrum may then accumulate in the vitreous and damage the retinal receptors and especially the macula.[29,30] It is also possible that cyanide may be present in relatively high concentration in the vitreous because of secretion by the ciliary epithelium or because of an affinity of cyanide for an ion such as potassium present in the vitreous.[29] The severe loss of visual acuity frequently encountered in this disease may also be explained by damage to the macula which is also relatively unprotected. Damage to the papillomacular bundle may explain the frequency of temporal pallor in this disease Progressive and continuous damage leads to complete optic atrophy. Combination of damage to papillomacular bundle and the peripheral retinal receptors may be expected to occur.

Demyelination occurs in the peripheral nerves in Nigerian tropical ataxic neuropathy[7,13] and probably also in other parts of the nervous system—especially the optic and auditory nerves and the spinal cord. Demyelination in optic nerves will explain the occasional finding of retrobulbar neuritis in the Nigerian patients. Chronic cyanide intoxication in experimental animals can produce demyelination.[7,13,19,31,32]

The ophthalmic findings in Leber's hereditary optic atrophy, subacute combined degeneration with optic atrophy, and tobacco

amblyopia, although vaguely similar in some respects, are in many ways different from those found in Nigerian ataxic neuropathy. It is worth recalling that there is some evidence suggesting that the visual impairment in these diseases is due to chronic cyanide intoxication.[11,33-35] However, ophthalmic findings similar to those described in the Nigerians with ataxic neuropathy have been described in tropical amblyopia in Jamaicans,[9] and in Jamaican neuropathy,[36] of which the former is probably a fragmentary form. Jamaican neuropathy is in many ways similar to the Nigerian ataxic neuropathy, although there are some subtle differences.[37] Recently,[29] bizarre and atypical visual field defects were described in Jamaican amblyopia, and although they were mostly unlike those described in tobacco amblyopia, in some cases there was some similarity. McKenzie and Phillip[29] (1968) state that there is no clear line dividing tobacco amblyopia from Jamaican amblyopia and nutritional amblyopia. The common factor may be chronic cyanide intoxication.

The evidence available at present does not suggest that the Nigerian ataxic neuropathy is related to disseminated sclerosis and neuromyelitis optica.[5] The former is virtually unkown in Nigerians; the latter, although quite frequently seen among Nigerians, is remarkably different in its clinical manifestations, presenting usually as acute retrobulbar neuritis preceding or following acute transverse myelitis.

Other causes of retrobulbar neuritis or optic atrophy associated with lesions elsewhere in the neuraxis were excluded in the Nigerians by the appropriate investigations. The list of possibilities is extensive and includes juvenile-onset diabetes with optic atrophy, acanthocytosis, Refsum's disease, Leber's hereditary optic atrophy, neurosyphilis, para-infectious encephalomyelitis, the heredofamilial spinocerebellar ataxais, peroneal musclar atrophy, familial opticoacoustic nerve degeneration and polyneuropathy,[38] and oculo-otocerebro-renal syndrome.[39]

Deficiency of thiamine, nicotinic acid, and riboflavin may produce the same abnormal biochemical end result in oxidative metabolism and in transfer or electron to molecular oxygen, as cyanide-induced inhibition of cytochrome oxidase, and hence may produce a similar neurologic picture. However, on clinical and biochemical evidence in the Nigerian patients with tropical ataxic neuropathy there is no deficiency of thiamine and nicotinic acid. Riboflavin deficiency, though it exists* in the Nigerian patients,[40] is so far not recognized nor has it been proved clinically or experimentally as a cause of polyneuropathy, myelopathy, and deafness,[41] although it may cause retrobulbar neuritis. Pernicious anemia is virtually unknown in the Nigerians,[42] and although there may be cyanide-conditioned deficiency of physiologically active vitamin $B_{12}$ in the Nigerian patients, this has no association with absence of an intrinsic factor.

The ophthalmic findings in Nigerian tropical amblyopia or tropical ataxic syndrome are consistent with the hypothesis that the major factor is a toxin. This toxin appears to be cyanide.

## Summary

In Nigerians, tropical amblyopia is a major component of a syndrome of tropical ataxic neuropathy which comprises bilateral optic atrophy, sensorineural deafness, myelopathy, and polyneuropathy. In a series of 360 Nigerian patients with this disease, more than 80% had visual signs and symptoms. In 18 patients, visual symptoms antedated other manifestations of the disease.

Severe impairment of visual acuity, sometimes progressing to complete blindness, bilateral temporal pallor, and complete optic atrophy were common findings. The commonest visual field loss was peripheral constriction (in 84%). Central or paracentral scotomas were uncommon. These suggest that retrobulbar neuritis was uncommon and

* New evidence confirms deficiency of riboflavin as determined by measurement of serum riboflavin.

that relatively unprotected retinal receptors in the periphery and the macula were damaged by a diffusible toxin. In the Nigerians, such a toxin is probably cyanide of dietary origin (from cassava meals).

ACKNOWLEDGMENT

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OPHTHALMIC MINIATURE

Sherlock Holmes welcomed her with the easy courtesy for which he was remarkable, and, having closed the door and bowed her into an armchair, he looked her over in the minute and yet abstracted fashion which was peculiar to him.

"Do you not find," he said, "that with your short sight it is a little trying to do so much typewriting?"

"I did at first," she answered, "but now I know where the letters are without looking." Then, suddenly realizing the full purport of his words, she gave a violent start and looked up, with fear and astonishment upon her broad, good-humoured face. "You've heard about me, Mr. Holmes," she cried, "else how could you know all that?". . . .

Sherlock Holmes clapped his hands softly together and chuckled.

"'Pon my word, Watson . . . . As you observe, this woman had plush upon her sleeves, which is a most useful material for showing traces. The double line a little above the wrist, where the typewritist presses against the table, was beautifully defined. The sewing-machine, of the hand type, leaves a similar mark, but only on the left arm, and on the side of it farthest from the thumb, instead of being right across the broadest part, as this was. I then glanced at her face, and, observing the dint of a pince-nez at either side of her nose, I ventured a remark upon short sight and typewriting, which seemed to surprise her."

Sir Arthur Conan Doyle
*A Case Of Identity*

# HYPERPLASTIC PERSISTENT PUPILLARY MEMBRANE

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*Toronto, Ontario, Canada*

A thick, persistent pupillary membrane covering the whole or most of the pupil is uncommon as a congenital anomaly. Most cases are sporadic. One author reports a pair of twins who were both affected.[1] This anomaly was transmitted by the autosomal dominant mode in three families.[2-4] In all of these the anomaly was associated with other ocular abnormalities such as cataract,[2-4] microcornea,[3] megalocornea,[4] nystagmus, either in the same individual or members of his family.

We describe a fourth family whose members have the same congenital anomaly (Fig. 1), but unassociated with any other ocular abnormality, except in one instance where the proband also had high myopia.

## CASE REPORT

The proband, a seven-year-old girl, was sent to our Eye Clinic by a school nurse because of poor vision in both eyes. The examination revealed severe myopia. Her corrected vision (—8.00 sph. in each eye) was 20/30 in the right eye and 20/60 in the left eye. There was an intermittent exotropia of 10 degrees. The pupils of both eyes were covered by a thick, raised, and slightly pigmented membrane (Fig. 2). The membrane consisted of a central area, about 4 mm in diameter and multiple peripheral strands, connecting this area to the collarette (Figs. 3 and 4). The lens itself appeared normal. The fundus viewed with the strong light of the indirect ophthalmoscope was normal.

### DESCRIPTION OF FAMILY MEMBERS

The proband's eldest sister had similar membranes covering the pupils of both eyes. Her best corrected vision was 20/80 in the right eye (correction: +1.75 sph.⊃+4.00 cyl. ax. 90°) and 20/30 in the left eye (correction: +1.00 sp.⊃+2.00 cyl. ax. 90°). She had an alternating exotropia of —10 degrees with a left hypertropia of two degrees. The lens and fundus were normal. At the age of eight years a sector iridectomy was performed on the right eye at the 12 o'clock position. Immediately the membrane shrank, leaving a wide open pupil (Fig. 5). Visual acuity was not improved by the operation. A postoperative iritis caused synechiae between the membrane and the lens.

The proband's three-year-old brother had similar pupillary membranes in both eyes. The visual acuity could not be measured, but no other ocular abnormalities were seen.

The mother, too, had similar pupillary membranes. Her visual acuity was 20/80 in the right eye, 20/30 in the left eye. All other members of the family examined including a maternal grandparent of the proband were normal.

## DISCUSSION

The four affected members of the family suffered from a condition called sometimes persistent pupillary membrane, or hyperplasia of the anterior layer of the iris stroma,[5] or hyperplasia of the iris.[6] The pupillary membrane, which normally exists during the third to the sixth month of fetal life is much thinner than that seen in this condition. Since there is no assurance that the condition is hyperplasia of the whole anterior layer of the iris, we suggest the term hyperplastic persistent pupillary membrane to distinguish it from "ordinary" persistent membrane which, though common, rarely has a familial inheritance.[7,8]

The thickness of the membranes and their

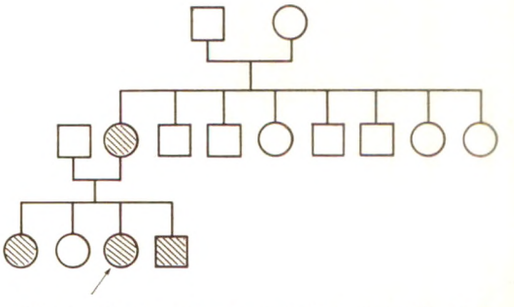


Fig. 1 (Merin, Crawford, and Cardarelli). Pedigree of family. Shaded circles and shaded square indicate members suffering from hyperplastic persistent pupillary membrane. Arrow indicates proband.

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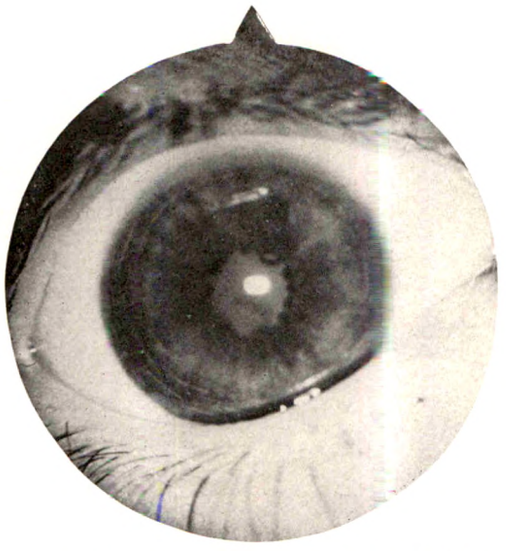


Fig. 2 (Merin, Crawford, and Cardarelli). Right eye of proband showing thick membrane covering almost the whole undilated pupil. The left eye was similar.

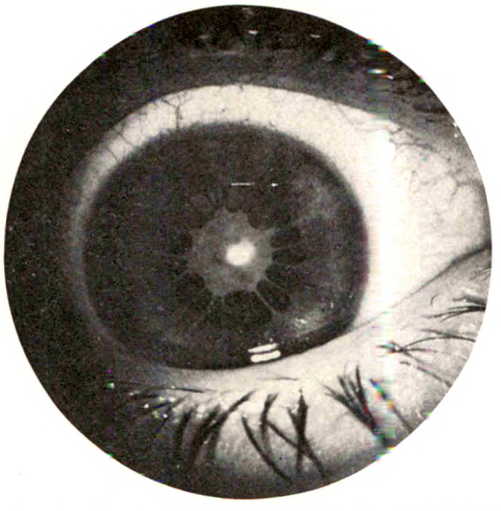


Fig. 3 (Merin, Crawford, and Cardarelli). Right eye of proband under maximum mydriasis.

opacity were striking, though visual acuity was remarkably good, ranging from 20/30 in the best eye to 20/80 in the worst.

Our one attempt to improve visual acuity by iridectomy failed. The results of a similar operation reported by Levy[9] are difficult to compare since preoperative visual acuity was unaided. Postoperative corrected visual acuity was 20/30 and 20/60, similar to that of our patients. Probably the condition should not be treated surgically except in very young children, before amblyopia develops.

The pedigree in our family points to an autosomal dominant mode of transmission of this anomaly, starting as a new mutation in the mother. Contrary to the other reported

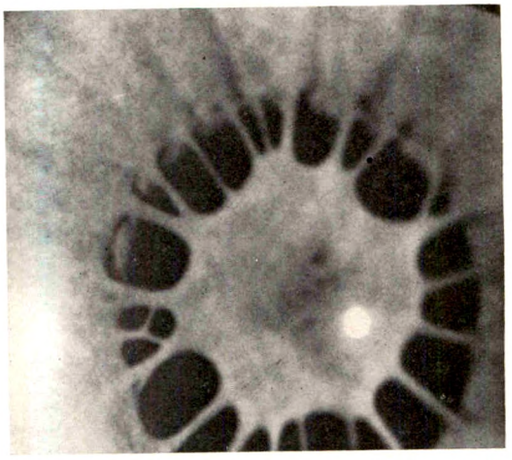


Fig. 4 (Merin, Crawford, and Cardarelli). Right eye of proband. Note the attachment of membrane to collarette.

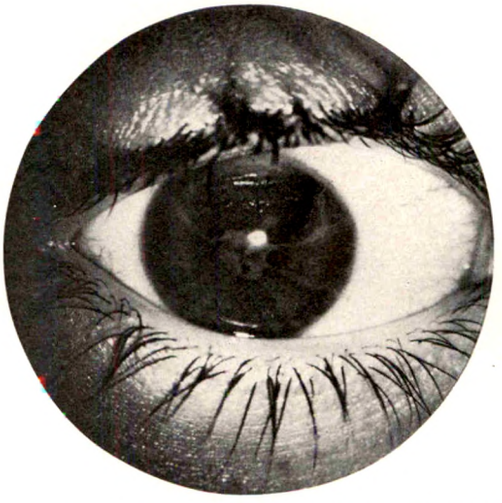


Fig. 5 (Merin, Crawford, and Cardarelli). Right eye of proband's eldest sister, showing optic iridectomy and shrunken membrane. Operation did not improve visual acuity.

families,[2-4] the anomaly in our family is isolated and not connected with corneal or lenticular abnormalities.

## Summary

A family is described with four members suffering from a condition termed as hyperplastic persistent pupillary membrane. This is the fourth description of a family with this condition. In all four the heredity was of the autosomal dominant mode. This is the first family reported without associated corneal or lenticular lesions.

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# PIGMENTARY RETINOPATHY OF MYOTONIC DYSTROPHY

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The common ocular findings in myotonic dystrophy include lenticular changes, blepharoptosis, extraocular muscle abnormalities, hypotony, and abnormalities of dark adaptation and the electroretinogram. Less frequently, pigmentary anomalies of the macula and peripheral retina are seen.[1-4] Histopathologic examination of the retina has been limited to investigations of specimens from six autopsies,[5-9] three of which demonstrated retinal pigmentary abnormality.[5,6] This paper presents the histopathologic findings in the retina of a patient with myotonic dystrophy and raises questions concerning possible pathogenetic mechanisms.

## CASE REPORT

A 44-year-old white woman was hospitalized at the Washington University Medical Center because of a left intraocular tumor. The patient had myotonic dystrophy for 20 years. She had taken a total of approximately 4700 g of quinine to the present time, but had none of the known toxic manifestations.

Examination revealed a best corrected visual acuity of 20/30 in the right eye and 20/70+1 in the left eye. There were multicolored posterior subcapsular opacities and normal intraocular pressures in both eyes. Both maculas showed pigmentary streaking. The fundi contained many clumps of pigment throughout the entire periphery. The pigment was not located adjacent to vessels nor did it resemble bone corpuscles. There was a large nonpigmented mass located in the inferior temporal quadrant of the left eye with an exudative retinal detachment inferiorly. Laboratory studies, including a VDRL, were normal. A diagnosis of malignant melanoma was made and the left eye was enucleated.

### HISTOPATHOLOGY

*Gross*—The specimen consists of a firm left eye measuring 22 × 22 × 24 mm with 6 mm of optic nerve attached. Transillumination reveals a poorly defined shadow at the insertion of the inferior oblique muscle. The globe is opened from 10 to four o'clock. The anterior segment appears normal. Scattered round pigment clumps in the retina are seen anterior to the equator (Fig. 1). There is a partially pigmented 7 × 7 × 6 mm tumor in the inferior temporal choroid.

*Microscopic*—The anterior segment is unremarkable except for thickening of the basement membrane of the ciliary epithelium. The lens is in place and shows posterior migration of subcapsular epithelial cells, bladder cell formation, and morgagnian globules. Arising from the temporal choroid between the equator and the optic nerve is a partially pigmented almond-shaped tumor composed of epithelioid cells and nucleolated spindle cells. The overlying retinal pigment epithelium is hyperplastic while the overlying retina is disorganized and contains cystoid spaces. There is a serous detachment of the neuroepithelium surrounding the tumor. The remaining choroid, sclera, and optic nerve appear unremarkable.

There is an artifactual detachment of the retina. The temporal retina anterior to the choroidal tumor and the nasal retina anterior to the equator exhibit diffuse cystoid degeneration and marked disarray of the layered architecture (Fig. 2). There is a loss of

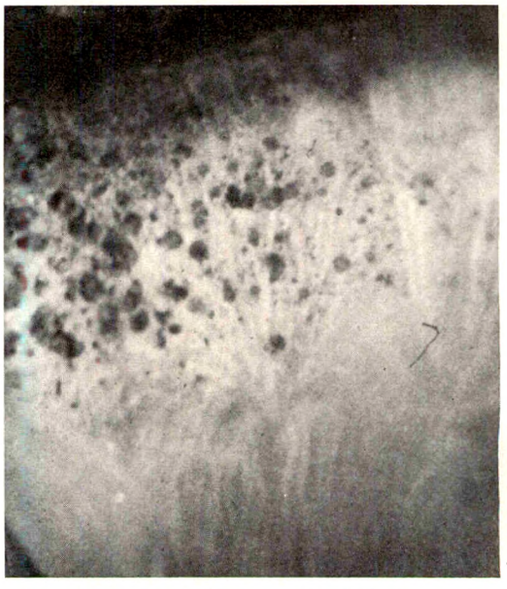


Fig. 1 (Betten, Bilchik, and Smith). Gross photograph showing clumps of pigment in the peripheral retina.

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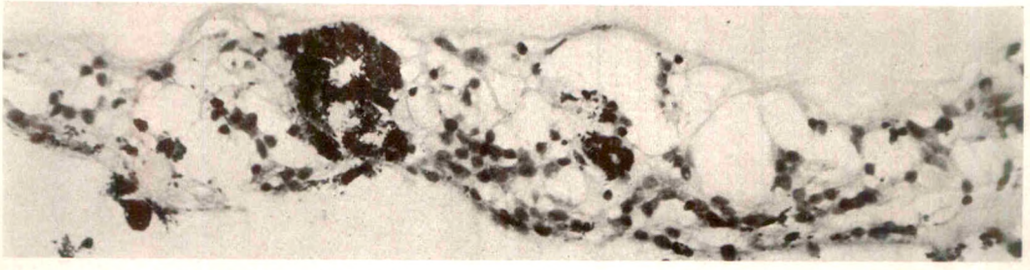


Fig. 2 (Betten, Bilchik, and Smith). Photomicrograph of peripheral retina demonstrating marked disorganization, cystoid spaces, loss of photoreceptors, and pigment migration. The pigment epithelium is artifactually detached (hematoxylin-eosin, ×350).

photoreceptors and, temporally, a reduction in the thickness of the inner plexiform layer. Foci of extracellular pigment and hyperplastic pigment epithelium are present within the retina frequently juxtaposed to areas where the retinal pigment epithelium is degranulated (Fig. 3). The intraretinal pigment is distributed throughout all retinal layers and is not located adjacent to vessels. There are foci of pigmented cells in the outer plexiform layer of the macula, which is otherwise intact (Fig. 4). Drusen of Bruch's membrane are scattered throughout the peripheral retina.

*Diagnosis*—Malignant melanoma of the choroid, peripheral pigmentary retinal degeneration, rare pigment migration into the macula, and cataractous lens.

## Comment

Verwey and Legras[10] first noted a pigmentary maculopathy in a patient with myotonic dystrophy. Since then, others[1-4] have encountered macular changes which often consist of streaks of pigment arranged in a stellate fashion. In some cases, reduction of visual acuity has been attributed to the macular changes.

A pigmentary abnormality of the peripheral retina in a patient with myotonic dystrophy was first described clinically by Gotfredsen.[11] His report, as well as subsequent papers,[1-4] describe a noncorpuscular, haphazard pigmentation in the retinal periphery.

Burian and Burns[1] studied 25 patients with myotonic dystrophy. Six patients had definite macular pigmentary changes and four of 13 examined with the indirect ophthalmoscope had pigment clumping in the periphery. Slatt[2] reviewed 17 patients with myotonic dystrophy. Four patients had grayish-white macular stippling but none had peripheral pigment deposition. Junge,[3] in a study of 52 patients with myotonic dystrophy, found pigmentary abnormalities in the macula of two patients and in the periphery of one patient. Babel and Tsacopoulos[4] reported the retinal findings in 12 patients with myotonic dystrophy. Eleven patients had a wide-meshed pigmentary network between the equator and ora serrata, and five patients had deep macular pigmentation.

Manschot[5] described the peripheral retinal histopathology in an autopsy specimen of a 48-year-old patient with myotonic dystrophy. His examination was limited by severe postmortem changes. There was marked atrophy of the external retinal layers and proliferative folds of pigment epithelium which extended into the retina. Hyaline material continuous with the thickened lamina vitrea filled the spaces within the pigment epithelial folds. There were numerous drusen of Bruch's membrane. Based upon these findings, Manschot hypothesized that pigment epithelial proliferation was the first stage in the retinal abnormality of myotonic dystrophy. However, his photomicrographs also

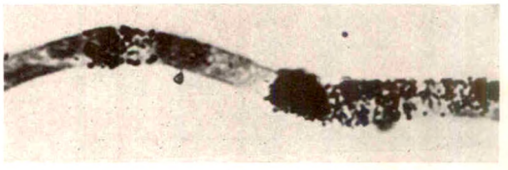


Fig. 3 (Betten, Bilchik, and Smith). Photomicrograph of peripheral retinal pigment epithelium showing areas of pigment degranulation (hematoxylin-eosin, ×720).

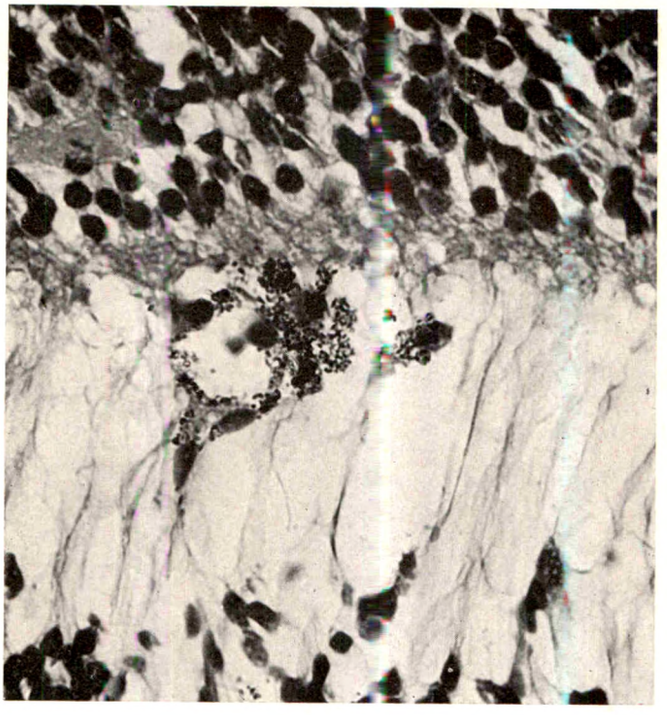


Fig. 4 (Betten, Bilchik, and Smith). Photomicrograph showing a focus of pigment cells in the outer plexiform layer of the macula (hematoxylin-eosin, ×720).

showed retinal degeneration in the areas of pigment epithelial proliferation.

Houbert and Babel[6] studied autopsy specimens from two patients with myotonic dystrophy. They found peripheral retinal degeneration and intraretinal pigmentary proliferation, as well as hyalinosis and microthrombosis of the peripheral retinal vessels.

Burns[7] found drusen of Bruch's membrane and central serous retinopathy in an autopsy specimen from a patient with myotonic dystrophy. The other two histopathologic studies in the literature[8,9] reported no retinal abnormalities.

The pathologic features in our case are generally similar to those described by Manschot[5] and Houbert and Babel.[6] In addition, we have observed areas of degranulation of an otherwise normal appearing retinal pigment epithelium and foci of pigmented cells in the outer plexiform layer of the macula.

On the basis of our observations, we cannot come to any definite conclusion concerning pathogenesis. The question which still remains is: Are these findings due to a primary neuro-epithelial disorder or are they secondary to a pigment epithelial disturbance? Another question is whether the retinal findings are indeed an intrinsic part of this multiphenotypic disease—i.e., myotonic dystrophy—or whether they are due to some other cause.

Since many patients with myotonic dystrophy take variable quantities of quinine during their life, is it possible that quinine may be responsible for the retinopathy? The idiosyncratic and overdose ocular reactions to quinine are an amblyopia with optic nerve atrophy, narrowed arterioles, and markedly constricted visual fields.[12] The pathogenesis of this toxic effect is not fully understood, but quinine, as discussed by Almeida,[13] is thought to either have a direct toxic effect on the retinal ganglion cells or an arteriolar narrowing effect leading to secondary retinal and optic nerve atrophy.

Quinine, by similar or perhaps different pathophysiologic mechanisms, may produce

other manifestations, such as those reported here, when the drug is taken steadily over a long period of time. One possible mechanism may involve binding of quinine or one of its breakdown products to melanin, with the subsequent development of retinal degeneration. It is known, however, that quinine is rapidly absorbed, degraded, excreted, and not accumulated in the body.[14] Yet, rapid handling and the lack of significant storage does not preclude sequestration of small amounts in selected tissues, e.g., the pigmented tissue of the eye. In support of this mechanism, Potts[15] found that quinine dihydrochloride, as well as a whole host of other resonating aromatic compounds, is bound in vitro to uveal melanin granules. To the best of our knowledge, an in vivo study of the affinity of quinine for melanin-containing tissue has not been done.

The chemical similarity of quinine and chloroquine,[14] the large accumulated dose of chloroquine necessary to produce retinopathy,[16] and the somewhat comparable histopathology observed in chloroquine retinopathy and our case (retinal localization differs),[17] further suggests to us that quinine may cause a tapetoretinal disease.

Clinical and laboratory studies seem indicated to probe this area of speculation. Investigation of the drug histories of patients with myotonic dystrophy with and without pigmentary retinopathy should help resolve the issue. Also, studies of patients taking other long-term quinolones (e.g., quinidine, the isomer of quinine) might also be informative.

## Summary

Gross examination of a surgically enucleated eye from a patient with myotonic dystrophy disclosed pigment clumps in the retina anterior to the equator. Microscopic study of the peripheral retina showed extensive pigmentary degeneration of the neuroepithelium and areas of proliferation and degranulation of the pigment epithelium. Rare foci of pigmented cells were observed in the macula. The possible role that quinine may have in producing this pigmentary retinopathy is discussed.

## Acknowledgment

Dr. Glen Johnston provided the clinical information in this case.

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# CONGENITAL AMAUROSIS OF RETINAL ORIGIN

## (LEBER)

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In 1869, Leber[1] described a disorder which included: (1) congenital amaurosis or highly imparied vision, (2) a fundus picture in infancy often showing marked discrepancy between this and the visual function, and (3) a recessive heredity. Subsequently an extinct, or nearly extinct, electroretinogram was described.[2] The ocular fundus in infancy may be either normal or demonstrate diffuse fine pigmentation. The condition often progresses to abnormalities such as those seen in retinitis pigmentosa.

The patients whose four case histories are described in this report are from a family of nine children. The mother was 36 years of age when the last child was born. There was no known consanguinity. Neither parent described a family history of mental retardation or eye problems. The first five children ranged from 16 to 21 years of age and were not available for eye examinations. They were described as normal, however, and although two of them had minor difficulties with schoolwork, they passed all school visual screening tests, obtained driver's licenses, and are gainfully employed without ocular complaints.

The four younger children all showed congenital retinal blindness associated with varying degrees of other ocular defects and mental retardation. In each of these cases, pregnancy and delivery were unremarkable.

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### CASE REPORTS

In all four of the cases described below, the following studies were performed and the results were declared normal: complete blood count, urinalysis, urine for amino acids, bilirubin, urine for reducing agents, and chromosomal karyotypes. Skull x-rays were also performed and these were also considered normal.

*Case* 1—This boy was born May 13, 1958. By the time he was six weeks of age, blindness was suspected by his parents. At three months of age he developed a "turned-in eye and jerking eye movements." He was first seen by our department at the age of seven years.

Ocular examination revealed normal eyelids with enophthalmos and minimal microphthalmos. Cornea, irides, and lenses were normal in appearance. Ophthalmoscopy revealed normal disks with slightly attenuated arterioles (Fig. 1). A repeat examination at the age of 10 years revealed a cataract in the left eye. Another examination was performed when he was 12 years of age revealed very fine retinal pigmentation which was not described in the early examinations.

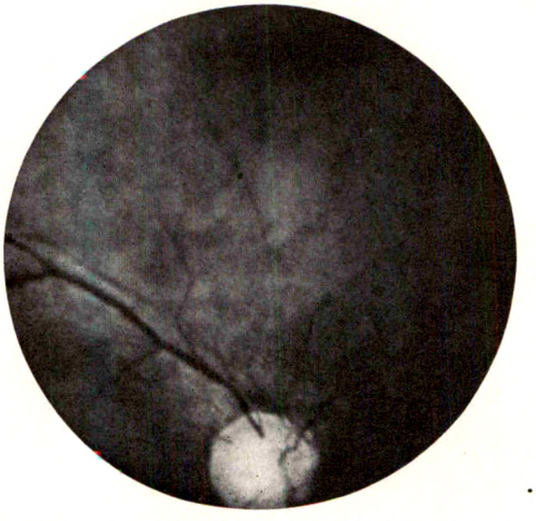


Fig. 1 (Edwards, Price, and Macdonald). Case 1. Left fundus illustrating attenuation of retinal arterioles and fine background pigmentation.

General physical examination revealed a child below the third percentile in height and weight with a borderline normal head circumference. There was a prominence along the sagittal suture. Muscle tone was generally increased. The remainder of the physical examination was unremarkable. An electroencephalogram revealed an irritative lesion in the left temporal area. Testing demonstrated low-normal intelligence. An electroretinogram, performed when he was 12 years of age, was extinguished. Shortly after his seventh birthday he was enrolled in the Kentucky School for the Blind where his over-all performance has been termed adequate.

*Case* 2—This boy was born April 29, 1960. Blindness was suspected by his parents at an early age. He was seen in consultation when he was five years of age. Ocular examination revealed enophthalmos. His right eye demonstrated a dense leukoma with adherent iris and flat anterior chamber. It was felt that this represented a perforated keratoconus. The left pupil reacted sluggishly to light. A moderately dense left cataract was present. The fundi were poorly visualized, but the disks appeared pale. At seven years of age he was re-evaluated and found to have bilateral dense cataracts. The fundi could no longer be seen.

General development was markedly delayed. The patient did not sit alone until the age of four years. Physical examination revealed a small child below the third percentile in height and weight. The head circumference was small with a prominence along the sagittal suture. Muscle tone was generally increased. The remainder of the physical examination was unremarkable. The only positive laboratory tests were a serum carotene level of 682 mg% and a blood sugar of 52 mg% reported at the age of five years. An electroencephalogram was moderately dysrhythmic. Evaluation at seven years of age revealed profound mental retardation.

*Case* 3—This girl was born July 12, 1961. Blindness was suspected by her parents by the age of two months. She was first seen in consultation at the age of four years. Eye examination revealed no fixation or following of light. Enophthalmos and microphthalmos were noted. The eyelids, corneas, irides, and anterior chambers appeared normal. The pupils showed hippus, but no light reaction. There was peripheral spoking of the lenses with cortical opacities. The disks appeared pale. She was re-examined at the age of seven years and found to have bilateral dense cataracts with no visualization of the fundi.

General development had been non-progressive after the age of one year. Physical examination revealed a small child with height, weight, and head circumference below the third percentile. There was generalized increased muscle tone, with the development of a positive Babinski sign on the right by seven years of age. The remainder of the physical examination was unremarkable. As in Case 2, blood chemistry revealed a markedly elevated serum carotene of 640 mg% and a blood sugar of 59 mg. An electroencephalogram revealed an irritative focus in the left frontal temporal region. Evaluation confirmed the impression of profound mental retardation.

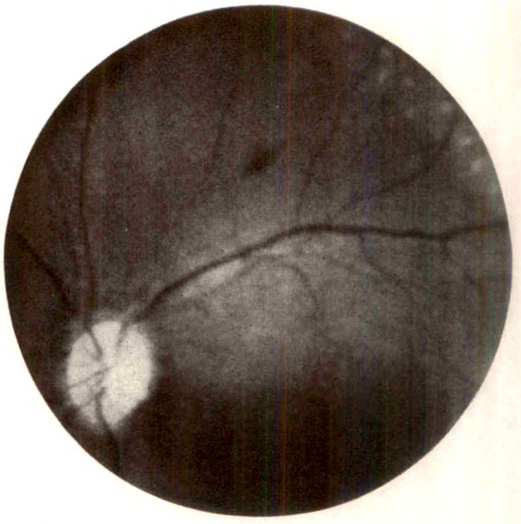


Fig. 2 (Edwards, Price, and Macdonald). Case 4. This photograph illustrates marked attenuation of retinal arterioles consistent with amaurosis congenita. The posterior pole appears normal. Adjacent is the abrupt commencement of the white punctate retinopathy.

*Case* 4—This girl was born May 12, 1964. Blindness was suspected by the age of one month. She was first seen in consultation at the age of 14 months. Eye examination revealed no fixation or following of light. Enophthalmos and minimal microphthalmos were evident. The eyelids, corneas, irides, anterior chambers, and lenses were normal. Fundus examination revealed normal disks and vasculature. Repeat eye examination at the age of four years showed fundi with attenuated arterioles and many small, discrete, flat, white, punctate lesions at the equator (Figs. 2 and 3). Some were irregular in shape. When she was re-examined at age six years of age, the punctate lesions were found to be yellow-white in color and tended to be larger and more irregular. The fundus appeared similar to a case reported by Krill.[6]

This child's general development was reported to be normal. Physical examination revealed height, weight, and head circumference below the third percentile. There was a prominence along the sagittal suture. In contrast to her three siblings, there was generalized hyporeflexia. An electroencephalogram showed an irritative focus in the left temporal region. An electroretinogram at the age of six years was extinguished. Evaluation revealed a probable low-normal intelligence. At the age of five years she was enrolled in the Kentucky School for the Blind where her progress has been good.



Fig. 3 (Edwards, Price, and Macdonald). Case 4. Area of left fundus showing areas of white punctate retinopathy.

## Discussion

In Leber's initial report[1] of this condition (1869), now termed amaurosis congenita, he described several children in an institution for the blind were he was the consulting ophthalmologist. He noted that the affected children were blind at birth or soon thereafter. The children also evidenced photophobia and nystagmus. A most interesting finding was that in the first few months of life no significant fundus abnormality could be seen. Later in life these children usually developed a fine pigmentation of the fundus. A few developed the typical bone spicule formation of retinitis pigmentosa, whereas a small number retained apparently normal fundi. Most of the patients, regardless of the background fundus picture, developed attenuation of the arterioles and the appearance of optic atrophy. Cataracts were noted in some of the older patients.

In the 100 years since Leber's report, others have added further relationships to the basic condition of congenital blindness of retinal origin. A significant proportion of the affected individuals are now known to have keratoconus or keratoglobus.[4-8] Alstrom and Olson[7] report an incidence of 33% in their oldest age group. A small series by Gillespie[8] reports an incidence of 100%. Leber[1] himself reported the low incidence of only 1% in a series of cases in young patients. Most authors feel the frequency of this association increases with age.

Electroretinographic study of these children is found to be severely abnormal, either extinct or characterized by minimal responses.[2,5,9,10,11] The digito-ocular phenomenon wherein blind children attempt manual retinal stimulation by pressure on their own globes is also seen in this condition.[12]

The family in this report illustrates that true congenital blindness of retinal origin is evident in early infancy. In each of these four children, blindness was suspected by the age of three months, and as early as the age of six weeks in one. Unfortunately, only one of these children (Case 4) was seen by us while still an infant. At that time, however, her fundus examination revealed no abnormality. The other three siblings had already developed fundus changes consistent with early optic atrophy by the time their initial eye examination was performed. All three had varying degrees of arteriolar attenuation associated with pale disks. One child (Case 1) has shown increasing fine pigmentation of the fundus without any clumping.

Retinitis punctata albescens has been described as part of the broad group of tapetoretinal degenerations. It has been suggested by Forsuis and Erikson[11] that it is part of a continuum between congenital retinal blindness and retinitis pigmentosa. These investigators state, however, that there is no report of retinitis punctata albescens appearing in a patient whose siblings have congenital blindness of retinal origin, as is the case in this family. In Case 4 in this report, as well as the case cited by Krill,[3] yellow-white spots are observed which are not necessarily related to retinitis punctata albescens or fundus albipunctatus.

The three eldest children in this study have developed cataracts (Fig. 2). In Case 1,

a unilateral cataract was found on examination at 10 years of age which was not present at the earlier examination when the child was seven years of age. In Case 2, cataract was present in one eye at the age of five years and was present bilaterally by the age of seven years. In Case 3, bilateral cataracts were developing at the age of four years and these had progressed to become dense by the age of seven years. Development of cataract seems related to age,[6,7,11] and our family confirms this concept. It is of interest that the two children who developed cataracts earliest are the two who are most severely retarded (Cases 2 and 3).

In various reports of keratoconus and keratoglubus[4-8] it appears that this disorder, like cataracts, becomes more evident with increasing age. One of our patients (Case 2) showed the probable aftermath of perforated keratoconus in one eye, demonstrating very clearly that it is possible to have corneal degeneration together with a typical fundus picture of congenital amaurosis.

Central nervous system disorders are variably reported in congenital amaurosis of retinal origin. Dekaban and Carr[10] felt that since the eye was intimately related to the brain developmentally, significant central nervous system defects might also be expected to occur with this entity. They presented seven affected children from four families and found only one to be normal mentally. Thee had epilepsy and two had abnormal electroencephalograms. Incidence of mental retardation and neuropsychiatric problems has ranged in various reports from 13% to 33%.[6] Some larger studies have excluded mentally retarded subjects and those with neuropsychiatric problems.[8] In this report, two of the four children affected are severely retarded (Cases 2 and 3), but all four of the children had abnormal electroencephalograms. Three of the children also demonstrate muscular hypertonicity while Case 4 demonstrates muscular hypotonicity.

In this family, the most severe eye problems (i.e., cataracts, keratoconus) were associated with profound mental retardation. The other two children, both of whom who are functioning well at the Kentucky School for the Blind (Cases 1 and 4), have clear media and minimal structural changes of anterior ocular segments. Waardenburg and Scappert-Kimmijser[13] made similar observations are made in their report of three sisters. However, there are several articles in which this parallel is not seen. Of the six retarded children presented by Dekaban and Carr[10] none had significant structural changes of the globe at the time of examination. In a family described by Gillespie,[6] four members had marked structural changes in the form of significant keratoconus, but none was mentally retarded. This points out the variability of expression of the gene of congenital retinal blindness, not only between affected families, but also within the affected families.

There have been several histopathologic descriptions of eyes with a clinical diagnosis of congenital retinal amaurosis. Aubineau[14] mentioned disorganization of the outer granular layer with loss of the receptive elements. He also described alteration of the pigment epithelium with pigment migration into the retina, thinning of the retina, and pronounced atrophy of the choriocapillaris. Sorsby and Williams[6] described "non-characteristic extensive degeneration of all retinal layers" in a 16-year-old patient. These authors felt that histopathologic examination of material from a younger patient would be needed to incriminate a specific retinal layer. Babel noted two specimens with extensive degeneration of the neuroepithelium and atrophy of the choroid in one eye.[15] What appeared to be an agenesis of rods only was described by Vrabec.[16] Waardenburg[4] reported an essentially normal neuroepithelium. In another paper, Gillespie[7] found a retina with no perceptive elements and peripheral areas with pigment migration, gliosis, and destruction of Bruch's membrane. In the posterior pole no rods or cones were seen, instead there was a "layer of cuboidal cells."

Congenital amaurosis of retinal origin is well accepted as a genetic entity. This family is compatible with the generally recognized autosomal recessive mode of inheritance.

There has been one instance of autosomal dominant inheritance reported. Sorsby and Williams[6] described a family in which members of three successive generations demonstrated congenital amaurosis of retinal origin.

Of interest is the report by Waardenburg and Shappert-Kimmijser[13] of a family in which both parents were affected with congenital amaurosis of retinal origin. They had two children, one boy and one girl, both of whom had normal eyes. These authors state that multiple alleles may be involved in determining the expression of congenital retinal blindness. This might explain the variability of expression between affected individuals.

Forsuis and Erickson[11] feel that congenital amaurosis of retinal origin and retinitis pigmentosa represent a continuum of tapetoretinal degenerations. They suggest, from their studies of tapetoretinal degenerations on the Åland Islands, that the various degrees of expression in that population may be due to a single genetic mutation hundreds of years ago.

## Summary

A family with four affected siblings demonstrates the variability of the fundus picture seen in congenital amaurosis of retinal origin. The four siblings in this study showed early severe decrease in visual function and attenuation of retinal arterioles. Of the two children who could be tested, both showed an extinguished electroretinogram. Two of the siblings revealed pigmentary changes of the retina. The unusual occurrence of a white punctate retinopathy in one child is thought to be part of the spectrum of congenital amaurosis. Three of the four siblings showed lenticular opacities and one demonstrated corneal degeneration. The progressive nature of both the fundus findings and the lens opacities in this syndrome is evident in this study, as is the association of mental retardation and congenital retinal blindness. Finally, this family illustrates the variability of both ocular and central nervous system defects in a sibship with diverse phenotypic expressions of this disorder.

### Acknowledgments

We thank Theodore Lawwill, M.D., for the electroretinograms in this study, Mr. Thomas Van Cader for the photographs, and Mrs. Linda Ballard for her secretarial assistance. We acknowledge with gratitude the assistance of the University of Louisville Child Evaluation Center and the Kentucky School for the Blind.

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# PERIPHERAL RETINAL ALBINOTIC SPOTS

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The pigment epithelium of the retina is one of the most reactive structures of the eye, and alternations in it are commonly seen in diseases and degenerative processes in the eye. The purpose of this report is to record the observation of a retinal pigment epithelial abnormality noted in the Eye Pathology Laboratory of The Johns Hopkins Hospital.

The abnormality was noted during the routine processing of autopsy eyes. One eye was from a 59-year-old white man who died of squamous-cell carcinoma of the esophagus, while the other eye was from a 64-year-old white man who died from complications of atherosclerosis. After the eyes were opened, it was noted that a round area of hypopigmentation was located inferonasally at the equator in one eye, and inferotemporally at the equator in the other. In each case, the fellow eye did not show similar abnormalities. The involved areas were characterized by a loss of pigmentation, a more distinct choroidal pattern, and by fairly well demarcated borders (Fig. 1). There was no juxtaposed area of pigmentary hyperplasia as is usually seen in old chorioretinal scars.

In each eye, only a single area was so involved. The spot measured 4 mm in diameter in one eye, and 4.5 mm in diameter in the other. Except for peripheral cystoid degeneration in both of the eyes and cobblestone degeneration in one eye, no other gross abnormalities were noted.

On microscopic examination of the involved areas, the cells of the retinal pigment epithelium were slightly flatter than in the uninvolved areas, as were the nuclei of the involved cells. These flattened cells had lost virtually all of their pigment granules. The few remaining pigment granules at the borders of the lesions appeared to have the lancet shape characteristic of the retinal pigment epithelium. A Fontant stain showed only the pigment which was obvious with other stains. In the areas directly bordering the lesion, the cells of the retinal pigment epithelium appeared entirely normal, the transition being a rather abrupt one (Fig. 2). Bruch's membrane, the choriocapillaris, and the remainder of the choroid directly underlying the lesions appeared normal. The overlying receptor elements and remaining retina were also normal. In one eye, drusen of Bruch's membrane were present in the hypo-

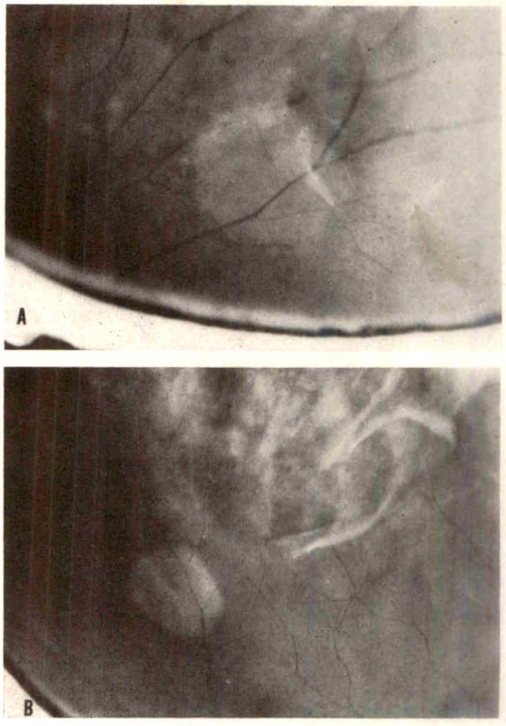



Fig. 1 (Schlernitzauer and Green). Gross photographs of the hypopigmented area noted in two autopsy eyes. Top: Eye of 59-year-old man. Bottom: Eye of 64-year-old man.

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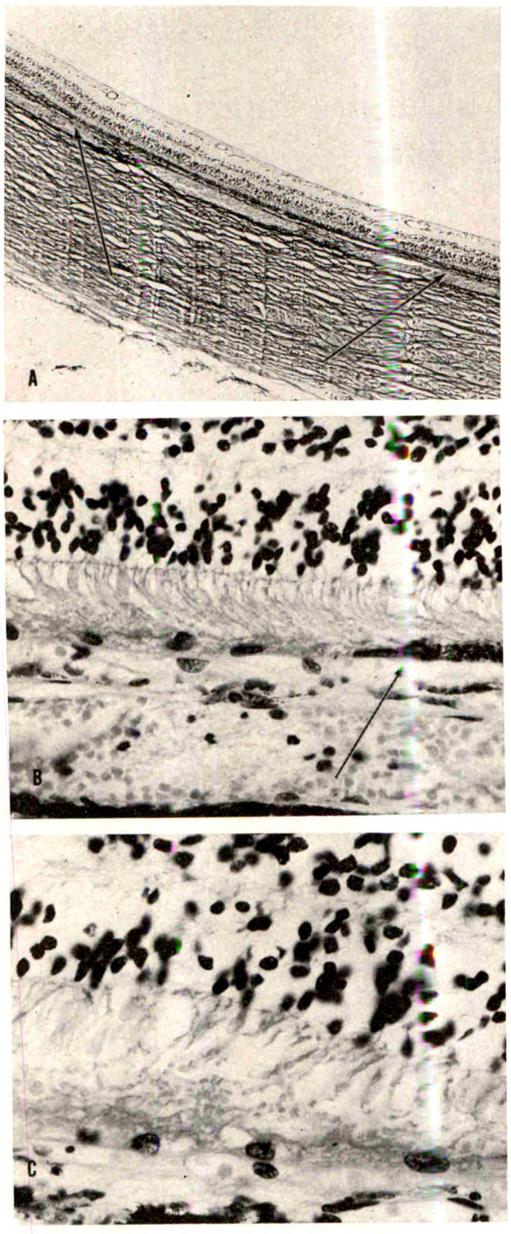



Fig. 2 (Schlernitzauer and Green). Photographs of the retinal pigment abnormality. Top: Overall view showing the extent of the lesion (arrows indicate the borders) (PAS, ×45). Center: Higher-power view of the border of the lesion, showing the abrupt transition from normal-appearing retinal pigment epithelial cells to the abnormal cells (arrow) (hematoxylin and eosin, ×575). Boston: View of the center of a lesion showing the somewhat flattened retinal pigment epithelial cells which lack pigment and which rest on a normal-appearing Bruch's membrane and choriocapillaris (hematoxylin and eosin, ×800).

pigmented area as well as in the uninvolved areas. The remainder of the eye was normal in both instances, except for mild arteriolarsclerosis of the retinal and choroidal vessels, and the peripheral cystoid degeneration and cobblestone degeneration noted above.

Although we are unable to make a clinicopathologic correlation at present, the clinical appearance of such focal areas of hypopigmentation might be similar to those depicted in Figure 3. These lesions were observed in six of 842 individuals examined during a mass screening of members of a small Maryland community.[1]

## Discussion

In 1921, Kraupa[2] reported on a variety of fundus lesions and he included a clinical drawing of a peripheral lesion which appears to be exactly the same as those we have observed. He was of the opinion that the lesion was most likely due to an acquired defect in the retinal pigment epithelium. In the same paper, however, he reported the occurrence of considerably smaller areas of pigment abnormality in the periphery, and he considered these to be probable congenital defects in the retinal pigment epithelium.

The unexplained absence of pigment granules in the retinal pigment epithelium was noted by Klien[3] in 1958 and was termed "depigmentation in situ." This designation was also used by Kurz and Zimmerman[4] in 1962 when they reported on vagaries of the retinal pigment epithelium. The process described by Klien, however, was in relation to diseases of the macula, and her paper does not note the occurrence of "depigmentation in situ" in the periphery. The histologic findings she described, however, are very similar to those reported in this paper. Klien suggested that this process—in which she had noted gradually expanding, ill-defined areas in which the choroidal vasculature became increasingly distinct over a period of months to years—may be a precursor of senile macular degeneration.

When areas of hypopigmentation occur in the periphery, on the other hand, as in the

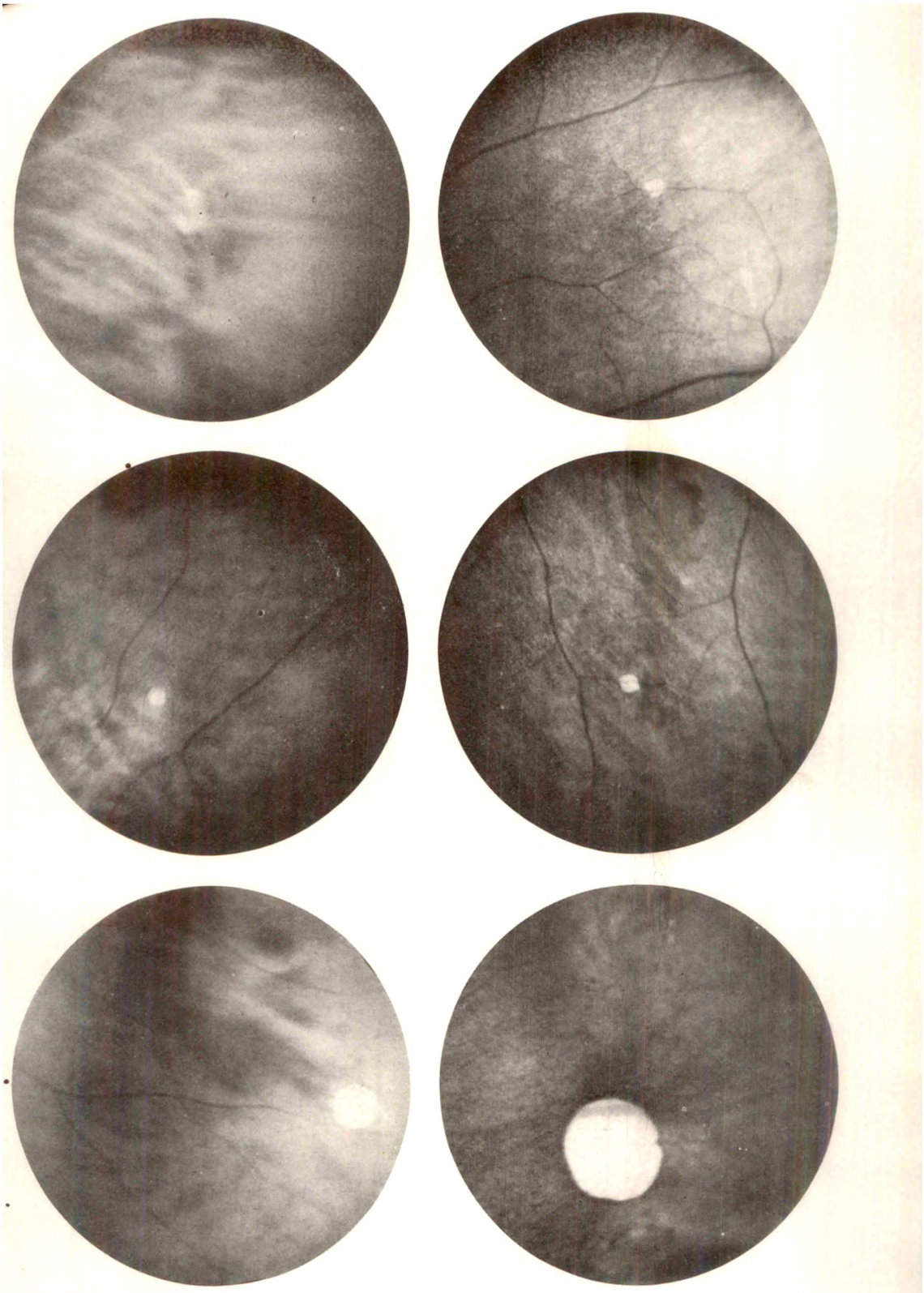


Fig. 3 (Schlernitzauer and Green). Photographs of the peripheral fundus in six patients showing well-demarcated, hypopigmented spots in which the choroidal vascular pattern is more prominent.

two cases reported here, it is difficult to project their evolution into any of the known peripheral lesions. Light microscopic evaluation of our specimens also leaves unanswered the question of the possible etiology of these changes. One of the more likely etiologies, perhaps, would be a localized vascular insufficiency, but no evidence has been found thus far to support this conjecture.

Realizing that in our two cases the development of the lesion had not been observed clinically, one cannot exclude the possibility of a congenital defect in the retinal pigment epithelium. It would therefore seem that until their pathogenesis has been ascertained it would be more suitable to use a term such as "peripheral retinal albinotic spots" to refer to this interesting (although perhaps not too significant) lesion of the retinal pigment epithelium.

## Summary

A peripheral area in the retinal pigment epithelium which was essentially devoid of pigment granules was noted during the routine processing of two autopsy eyes. A light-microscopic description of the abnormality is presented, but no conclusion as to the etiology of the lesion is offered. Since the possibility exists that these lesions are congenital rather than being degenerative, it is suggested that they be termed "peripheral retinal albinotic spots" to distinguish them from histologically similar lesions which have been observed to develop in the posterior pole by a process that has been termed "depigmentation in situ." Probable clinical counterparts of the peripheral retinal lesions reported here have been observed.

### Acknowledgment

We thank Dr. Robert A. Prendergast for his help in review of this manuscript.

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# EFFECTS OF TOXOPLASMA GONDII TOXIN ON THE RABBIT EYE

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Weinmann and Klatchko[1] first observed in 1950 that a toxin probably is present in the peritoneal fluid of mice previously infected with the RH strain of Toxoplasma gondii. They gave an intravenous injection of 0.1 ml of supernatant fluid from centrifuged peritoneal exudate to healthy Swiss mice. This resulted in severe respiratory symptoms, convulsions, and death. However, a dose of five times this amount injected intraperitoneally was tolerated by the mice.

Weinmann[2] later observed this toxin had no hemolytic or anticholinesterase activity and no antigenic properties and that it was thermostable. He also demonstrated that a similar ascitic fluid induced by chemical (lactic acid) or biologic (killed streptococci, tumor grafts) means produced no disease when injected intravenously in mice.

Varela and co-workers[3] believed that the toxic action of the centrifuged fluid resulted from the presence of a substance resembling the diethyl-amide of D-lysergic acid, while Pettersen[4] believed that the toxic effect was nonspecific and that it was caused by substances that originated in the mice.

According to Nozik and O'Connor,[5] the lethal effects produced in mice by the supernatant fluids from Toxoplasma-induced mouse peritoneal exudates can be positively correlated with the viscosity and surface-tension characteristics of this fluid.

Zardi recently was able to obtain and report on a purified preparation of the toxin of Toxoplasma gondii by a newly developed method.[6] This toxin was found to have the biologic actions of a true toxin. We are reporting here some clinical and histologic studies of the effects of this toxin on the rabbit eye after it was injected into the anterior chamber and the vitreous humor.

## Materials and methods

*Preparation of toxin and control*—Two-month-old white Swiss mice, each weighing about 20 g, were injected intraperitoneally with 15 million organisms of the LP strain of Toxoplasma gondii. This strain originally was isolated from the hypothalamus of a newborn hydrocephalic human infant and was maintained in mice by intraperitoneal inoculation. The virulence and antigenic properties of this LP strain are similar to those of the RH strain. After five days the peritoneal exudate was removed and subjected to ultracentrifugation at 31,000 × G. The supernatant fluid containing the toxin was adsorbed with trypsinized anti-mouse guinea pig spleen cells in order to remove proteins of mouse origin. The nitrogen content of the supernatant fluid measured by the micro-Kjeldahl method was 2.45 g/100 ml before the adsorption and 1.86 g/100 ml afterward. No mouse protein could be detected in this supernatant fluid by immunodiffusion against rabbit anti-mouse serum. The fluid was lyophilized at − 30°. and then resuspended to a concentration of 400 mg/ml in sterile distilled water buffered with phosphate at pH 7. The solution was then dia-

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TABLE 1

SCHEDULE OF ENUCLEATION IN 19 RABBITS RECEIVING ANTERIOR CHAMBER INOCULATION

| No. Rabbits | Time Elapsing before Sacrificing (in days) |
|---|---|
| 3 | Retained |
| 3 | ½ |
| 3 | 1 |
| 3 | 1½ |
| 2 | 2 |
| 1 | 3 |
| 1 | 4 |
| 2 | 7 |
| 1 | 27 |

lyzed through one-fourth inch Visking tubing against the same amount of distilled water; this procedure was repeated three times. The dialysate at the end of this procedure was tripled in volume: it was again lyophilized, then resuspended at a concentration of 400 mg/ml in distilled water buffered with phosphate at pH 7. The solution had a viscosity of 1.23 centipoises at 20°C.

The same procedure was adopted for preparation of the control peritoneal exudate which was produced by injecting 0.5 ml of sterile culture broth, 0.5 ml of a solution of sterile tapioca powder at the concentration of 1.0g/100 ml or 0.2 ml of a streptococcal extract prepared in the following way: five billion beta hemolytic streptococci per ml of sterile distilled water were heated for 15 minutes at 100°C and then centrifugated at 2000 × G for 20 minutes. The supernatant was injected into the peritoneal cavity. The control peritoneal exudate was centrifuged, adsorbed and lyophilized as described for the Toxoplasma induced exudate. The lyophilized powder was dissolved at a concentration of 400 mg per 100 ml in sterile distilled water buffered with phosphate at pH 7.

There was no difference in the morphology of the cells of the exudate produced by Toxoplasma gondii and that produced by broth, tapioca or streptococcal extract. No mouse proteins were detected in the control peritoneal exudate after absorption with trypsinized anti-mouse guinea pig spleen cells, when tested by immunodiffusion with rabbit anti-mouse serum.

*Anterior chamber injection*—Nineteen pigmented rabbits, each weighing about 2.5 kg, were inoculated with 0.1 ml toxin in the anterior chamber of the right eye and with 0.1 ml of control fluid in the left eye. The eyes were enucleated according to the schedule shown in Table 1.

The rabbits were anesthetized with pentobarbital sodium and given a retrobulbar injection of carbocaine in 1.5% solution. A 7-0 black silk suture was placed intracorneally near the upper limbus, and a 27-gauge needle then was passed through an intracorneal track, superficial to the suture, into the anterior chamber. Aqueous humor was removed and replaced with 0.15 ml of toxin or control fluid. As the needle was withdrawn from the chamber, the intracorneal suture was tied, preventing loss of fluid. The rabbits were examined daily with a flashlight, ophthalmoscope and slit lamp microscope.

*Vitreous injection*—Twenty rabbits were inoculated with 0.1 ml of toxin in the vitreous of the right eye and with 0.1 ml of control fluid in the left eye. The eyes were enucleated according to the schedule shown in Table 2. The rabbits were anesthetized, and the anterior chamber was emptied of aqueous humor with a syringe and 27-gauge needle. Using another syringe and 27-gauge needle, the toxin and control fluids were injected either into the anterior or posterior vitreous through a puncture in the superior pars plana region. A silk suture was inserted at the injection site for identification at the time of histologic study. The rabbits were examined daily with the slit lamp and ophthalmoscope.

All eyes were enucleated shortly after sacrifice, fixed for 48 hours in neutral 10% formalin solution and washed for 24 hours in running tap water. Large nasal and tiny temporal calottes were then removed and the eyes were processed in the usual manner in paraffin. Step sections were studied at various levels in the two calottes and the central

portion. Mallory and van Gieson stains were applied to some sections, but routine sections were stained with hematoxylin and eosin. Occasionally, sections from the eyes given an anterior chamber injection were stained with PAS to show the changes in the iris and deep corneal stroma.

## Results

### Clinical findings

*Anterior chamber injection of toxin*—Within three to six hours there was some chemosis with cells and flare and a fibrin clot in the anterior chamber. This increased up to 24 hours and was accompanied by a variable amount of corneal edema. Posterior synechias of the iris to the lens invariably occurred. The signs persisted for three to four days, then slowly subsided. By the seventh to tenth day the inflammation was gone and synechias, iris atrophy and anterior subcapsular cataractous changes in the lens were observed. Glaucoma and keratectasia occurred in one-third of the eyes.

*Control eyes*—The control eyes showed a mild iridocyclitis for one to two days and then became quiet.

*Vitreous injection of toxin*—Within 24 hours there was some iridocyclitis but no fibrin clot or chemosis. The anterior or posterior vitreous showed a gray, hazy opacification so that the retina was difficult to see. This grayness often was more intense in the inferior vitreous. In a few eyes, small vitreous hemorrhages occurred because of the ciliary body necrosis. The vitreous haze usually cleared during the subsequent one to two weeks, at which time there were pigmented chorioretinal scars. The scars were usually more severe inferiorly, but quite often they were found to be diffuse. A cataract secondary to the inflammation developed in eight eyes.

*Control eyes*—The control eyes showed some cells in the vitreous and a few tiny hemorrhages, but there was no important inflammatory reaction and the vitreous remained quite clear. Slit lamp examination of the anterior eye was always negative.

TABLE 2

Schedule of enucleation in 20 rabbits receiving vitreous inoculation

| No. Rabbits | Time Elapsing before Sacrificing (in days) |
|---|---|
| 2 | Retained |
| 3 | ½ |
| 3 | 1 |
| 3 | 1½ |
| 2 | 2 |
| 1 | 3 |
| 1 | 4 |
| 2 | 15 |
| 2 | 20 |
| 1 | 25 |

### Histopathologic findings

*Anterior chamber injection of the toxin.* The following changes were seen in eyes removed 12 hours to three days after inoculation. Within 12 hours there was a diffuse or localized keratoconjunctivitis and episcleral, scleral and trabecular inflammation. These tissues showed edema and infiltration of polymorphonuclear leukocytes. Some eyes showed a large fibrin clot containing polymorphonuclear leukocytes in the anterior chamber.

The anterior iris layers were involved earliest (Figs. 1 and 2). There was stromal edema and the melanocytes were swollen and rounded. The vessels were quite congested and their lumina often were occluded by thrombi (Fig. 1). The vascular endothelial cells were swollen and pale; their nuclei were absent or stained poorly. The vessel walls also showed edema and disruption (Figs. 1 and 2). Hemorrhage into the stroma of the pupillary and ciliary portions of the iris and into the stroma of the ciliary processes was frequent (Fig. 1). Polymorphonuclear leukocytes often were seen in the anterior half of the edematous stroma. The epithelial layers of the posterior iris and anterior ciliary body almost always showed

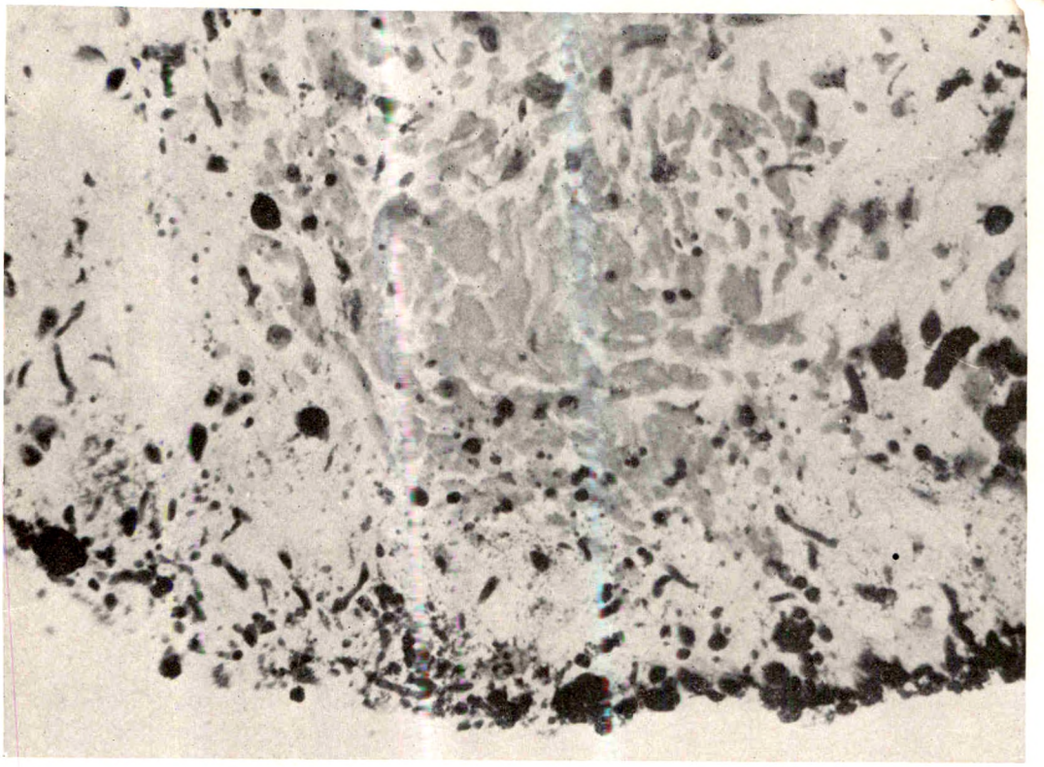
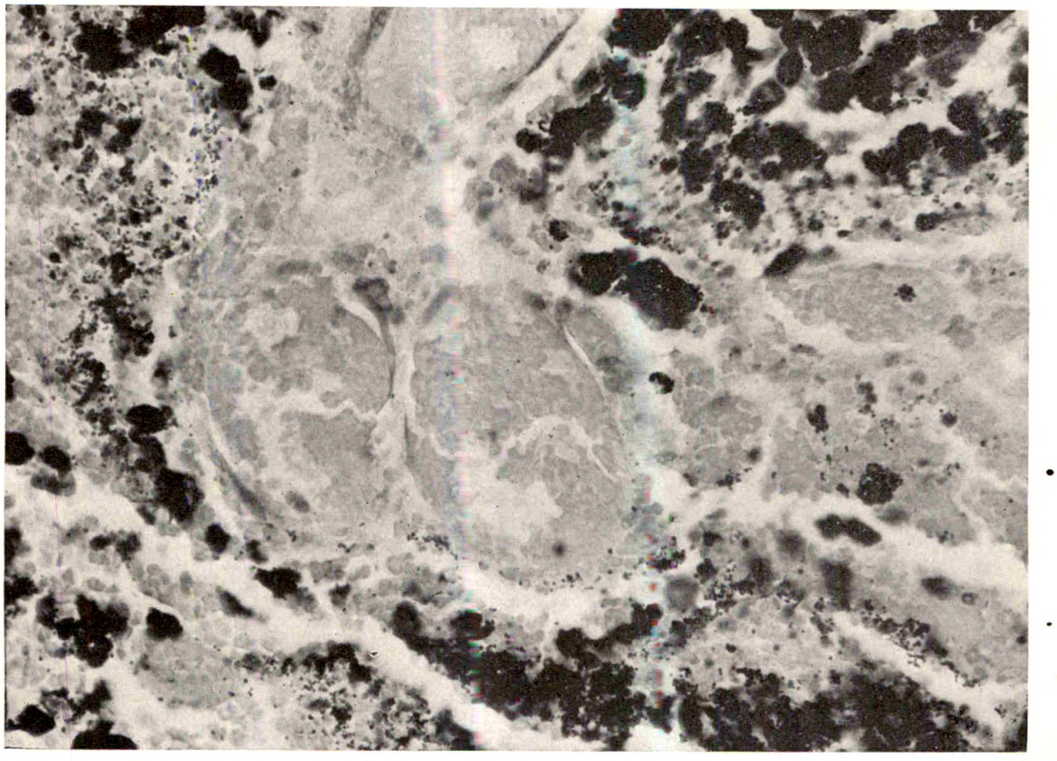


Fig. 1. (Hogan, Moschini, and Zardi). Acute iritis with stromal necrosis, hemorrhage, and degeneration of the posterior epithelial layers (×100).



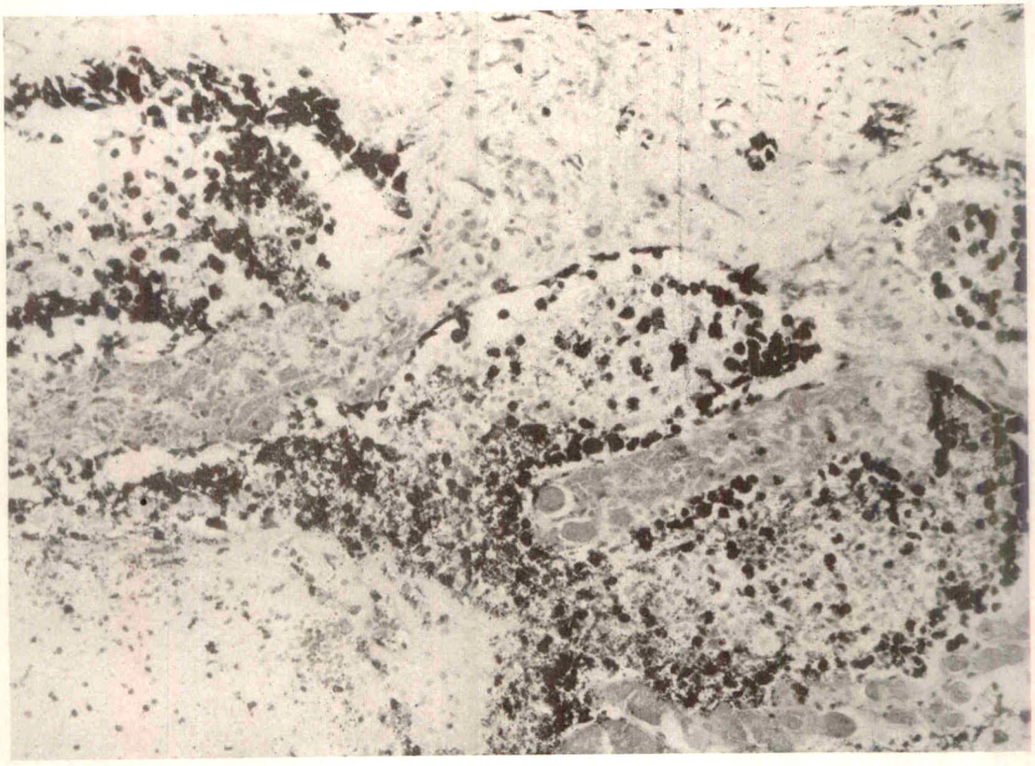


Fig. 3 (Hogan, Moschini, and Zardi). Acute cyclitis with necrosis of the ciliary processes, vascular destruction, thrombosis and stromal hemorrhage. There is marked destruction of the epithelial layers with pigment dispersion (×40).

edema and degeneration and frequently were separated from the stroma.

Many eyes showed similar vascular and stromal changes in the ciliary body. Hemorrhage was frequent in the disintegrating ciliary processes and posterior chamber. In some eyes the stromal and epithelial necrosis in the ciliary body was so marked that only engorged, thrombosed vessels remained. Pigment from the disintegrated stromal melanocytes and epithelium was dispersed in fine granules through the affected stroma and ciliary processes (Figs. 3 and 4).

Cataract occurred in many eyes, but the changes are believed to be caused by the adjacent inflammation. Reparative changes were found after the first three days. The anterior third of the iris stroma became less vascular and more fibrosed, and a characteristic group of large, rounded pigmented macrophages or damaged melanocytes occupied this area (Fig. 5). The ciliary body showed marked degenerative changes in the processes and stroma with pigment dispersal in the posterior chamber (Fig. 6).

*Vitreous injection of toxin*—The following changes were seen in eyes removed 12 to 36 hours after inoculation:

1. *Anterior vitreous injection*—If the Toxoplasma toxin was placed in the anterior vitreous, a short distance behind the lens, the principal effects in the ciliary body was similar to those after anterior chamber injection. The retinal changes varied; in some areas

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Fig. 2 (Hogan, Moschini, and Zardi). Same as Figure 1. Destruction of the vessel walls, stromal hemorrhage, pigment and stromal cellular destruction (×100).

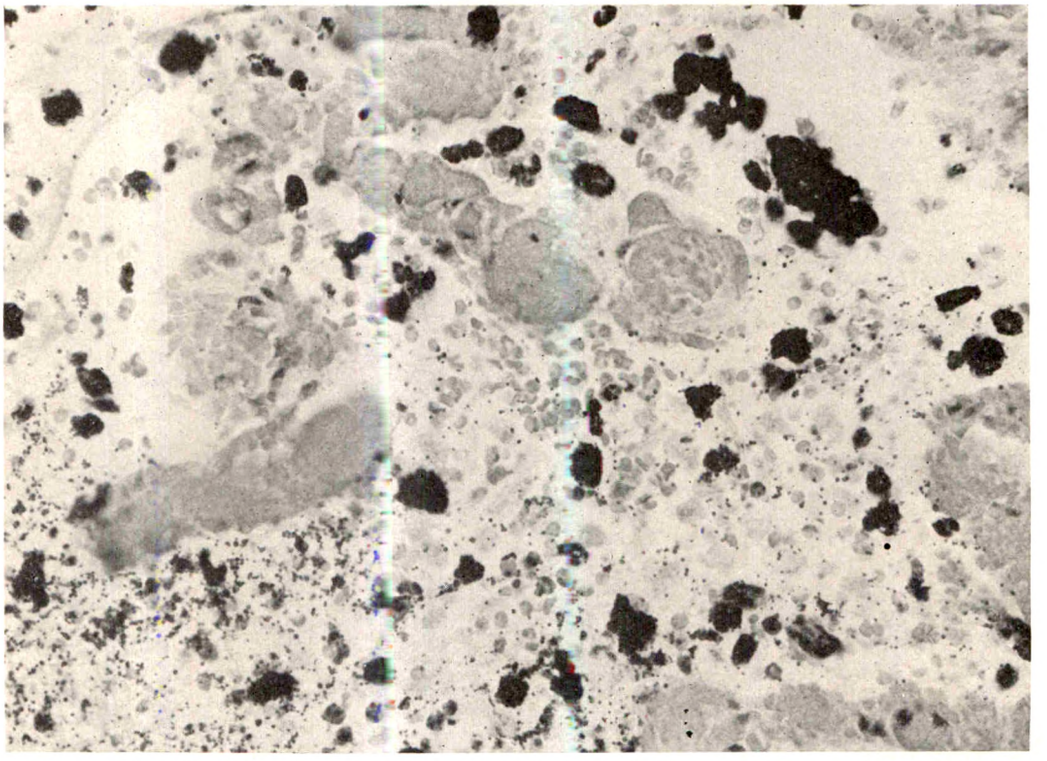
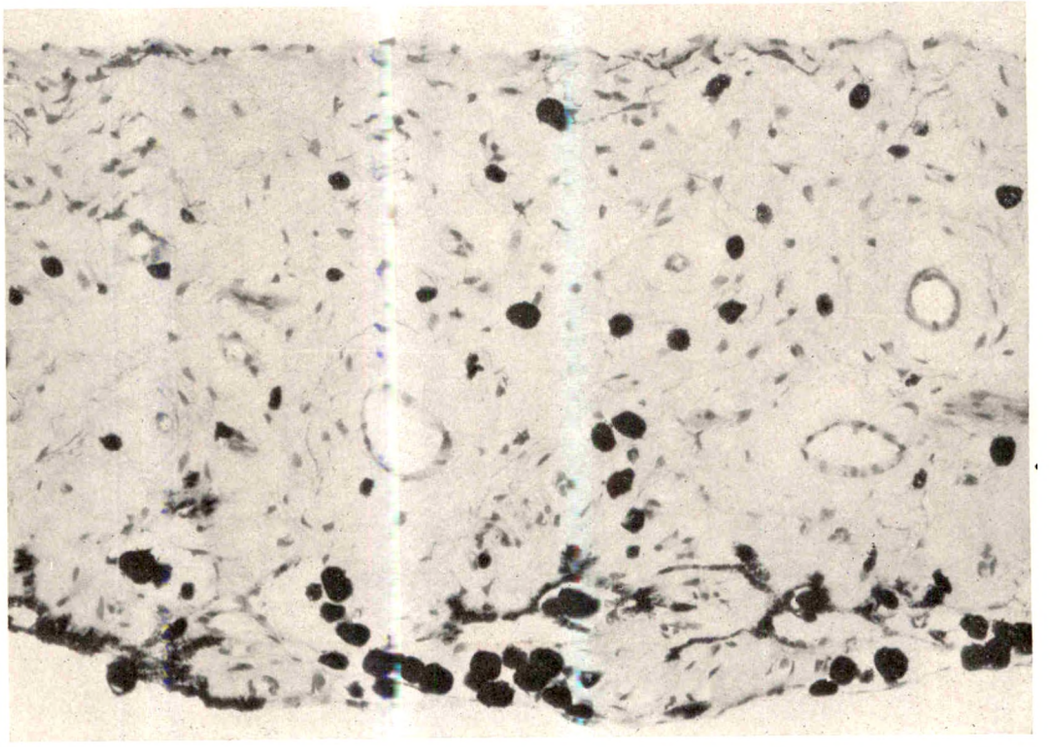


Fig. 4 (Hogan, Moschini, and Zard). Same as Figure 3, showing the vascular and stromal damage (×100).



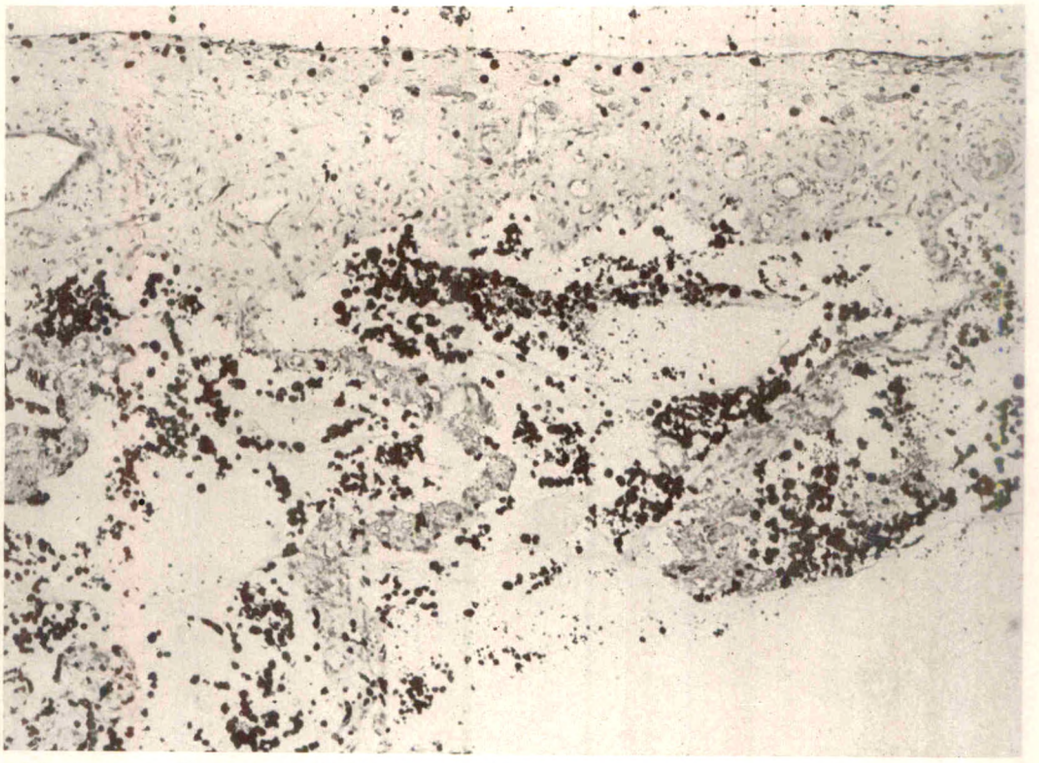


Fig. 6 (Hogan, Moschini, and Zardi). Healed iris and ciliary body lesions. There is severe damage to the ciliary processes with loss of epithelium and blood vessels (×22).

the innermost layers of cells and nerve fiber layer were severely damaged and infiltrated with polymorphonuclear leukocytes and lymphocytes being replaced by scattered inflammatory cells. In other areas the entire retina including the pigment epithelium showed severe destruction. The nuclear layers were swollen, and their nuclei were more basophilic. The outer segments of the receptors were replaced by a granular debris and the pigment epithelial cells were swollen, misshapen and dislodged from their normal position (Fig. 7).

The choroidal vessels were distinctly congested, and the stroma frequently contained hemorrhages. In the posterior eye the retinal vessels showed few changes; there was no congestion and very little infiltration with inflammatory cells. After the first two to three days there was no progression of the inflammatory process and formation of chorio-retinal scars soon became apparent (Fig. 8).

2. *Posterior vitreous injection*—In most eyes the injection was at a site just posterior to the center of the vitreous. In these eyes, the changes were localized to the choroid and retina, except for ciliary congestion in a few eyes. The changes in the retina and choroid were identical to those seen when the injection was made into the anterior vitreous, ex-

Fig. 5 (Hogan, Moschini, and Zardi). Late reparative phase in the iris. There is stromal and epithelial pigment cell loss, and stromal scarring. Some vessels have been obliterated, while others have a reduced caliber (×50).

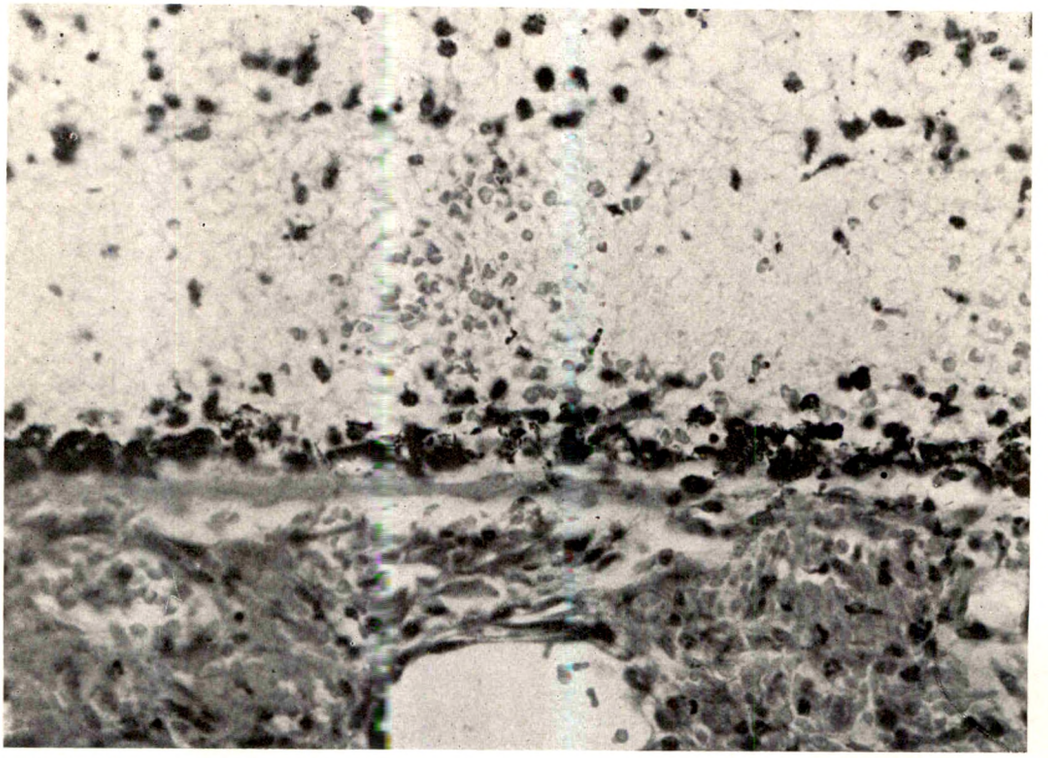


Fig. 7 (Hogan, Moschini, and Zardi). Acute chorioretinitis. The retina shows marked cellular destruction with hemorrhage. The pigment epithelium is degenerating. The choroid shows marked congestion and some stromal hemorrhage (×100).

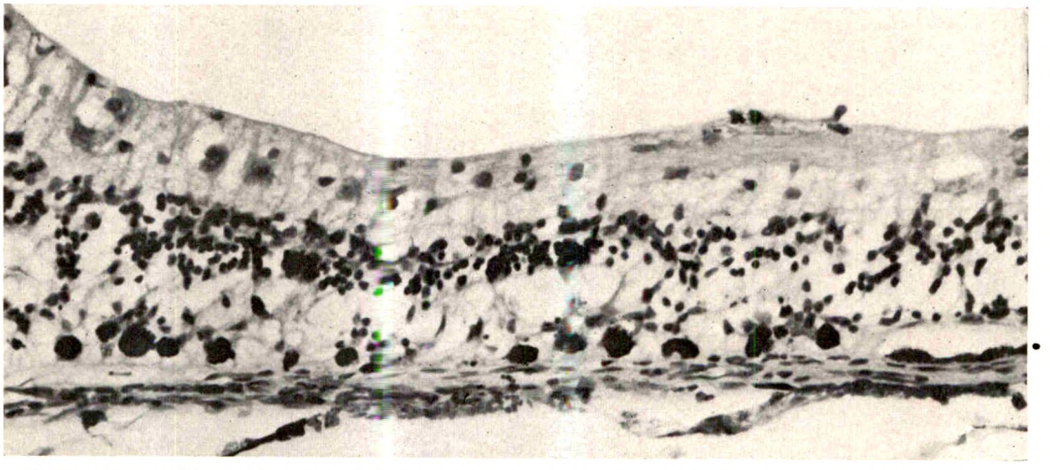


Fig. 8 (Hogan, Moschini, and Zardi). Healed chorioretinal lesion. The retina shows marked degenerative changes and is united to the choroid by cellular scar tissue. The internal choroid also shows some scarring (×64).

cept for involvement of the vessels on the inner retinal surface and disc region. These vessels showed more congestion and perivascular polymorphonuclear leukocytic infiltration. In the healed stage, a variable amount of retinal and choroidal destruction with scar formation was seen.

The amount of involvement of the retina and choroid seemed to depend on the exact placement of the injected fluid and the eventual distribution of the toxin; the entire area of these two tissues rarely was involved.

*Control eyes*—All of the control eyes were unremarkable. Some inflammatory cells were observed in the vitreous for two to three days after vitreous injection of the control fluid.

## Discussion

The histologic findings in these eyes show that when this product of Toxoplasma gondii-induced peritoneal fluid is injected into the rabbit eye the vascular and cellular effects suggestive of a real toxin are observed. In common with other known toxins, this preparation produces an irreversible alteration of the cell structure either by changes in the cell membrane or cell metabolism. It is well known that every toxin has a different mechanism of action. Pappenheimer,[7] for instance, has accumulated evidence that the toxicity of diphtheria toxin results from its interference with the cytochrome system of the cells of susceptible animals. The toxin of Clostridium perfringens is a lecithinase, an enzyme which cleaves phospholipid substrates to yield phosphorilcholine and diglycerides, thus altering the cell metabolism.[8]

In the present series of experiments, the vascular endothelium of the iris and ciliary body was found to be most severely affected. The vascular changes were characterized by thrombosis and disruption of the vessel walls. The dose of toxin administered here probably is greatly in excess of that which would be produced by the Toxoplasma organisms in the ordinary toxoplasmic lesion. Nevertheless, the cytologic effects on the cells is similar to that seen in tissue cultures where nonparasitized cells are affected by some product of the proliferating organisms.

The ocular tissue changes produced by the toxin injected into the vitreous are similar to those seen in toxoplasmic infections of the retina. It may be that the severe necrosis that occurs in toxoplasmic infections is caused by the liberation of toxoplasma toxin.

The elucidation of the biochemical mechanism of the action of Toxoplasma gondii toxin was not among the aims of our report; further studies are required in this area.

## Summary

A toxic material was prepared from Toxoplasma-infected peritoneal fluid of white mice by ultracentrifugation, absorption with anti-mouse guinea pig spleen cells, and repeated lyophilization and dialysis against distilled water. It was finally suspended in distilled water as a clear, nonviscous sterile solution. Control peritoneal fluid was produced by peritoneal injection of sterile broth, tapioca, or streptococcal extracts and treated in the same way. Anterior chamber and vitreal injection of this toxin produced necrosis of the vascular endothelium of the iris and ciliary body. It also destroyed fibroblasts, melanocytes, neuronal and glial cells, and bleeding occurred as a result of vascular changes. Control fluids produced no such changes. The cellular effects are those of a toxin and are similar to the necrotizing lesions seen in acute toxoplasmosis.

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## Ophthalmic miniature

Every schoolboy knows that the termination *-itis* indicates inflammation, and it is rather a shock to those of them who become medical students, when they start pathology, and have inflammation described to them in great detail, to find that a lot of -itises (or itides) are by no means inflammatory. It is not merely conditions like chronic nephritis, appendicitis, and cholecystitis, which (though they commonly have no persisting inflammatory element) have at least the excuse that they are usually the sequelae of active inflammation, but there are conditions such as osteoarthritis, osteitis deformans, and osteitis fibrosa cystica in which there is no pretence of any inflammatory element. It is all very confusing for the student.

The odd thing is that etymologically speaking osteoarthritis is just as correct as peritonitis. To quote O.E.D.: "Greek *itis,* properly forming the feminine of (certain) adjectives, but often used substantively . . . as in Lake Asphaltis; (also) in Greek, used to qualify (disease) of the joints, etc." So in saying osteoarthritis, we are, strictly speaking, indicating the presence only of disease of bone and joint together, not of inflammation.

This piece of history should not, however, have any influence at all on our opinions as to present usage. We have established that *-itis* refers to inflammatory conditions, and we ought to stick to this. At least it is unlikely that anyone will knowingly coin any new noninflammatory uses. Where there are sound alternatives, as with osteitis deformans and cystica, we ought to prefer them. Where it is possible without confusion, we might encourage a shift to the neutral *-osis*—perhaps even osteoarthrosis. For old scarred organs, we might prefer such a term as fibrosis of the appendix to the implication of chronic inflammation. It is a mistake to try to reform a language overnight, but there is no harm in encouraging a process of attrition.

Reflections of a Lexicographer
*Lancet,* 1971

# ANEURYSM OF THE OPHTHALMIC ARTERY WITH DRUSEN OF THE OPTIC NERVE HEAD

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Drusen (hyaline bodies) in the optic nerve head may be responsible for defects in the visual fields,[1] and rarely, they are associated with tumors and other diseases of the intracranial structures.[2-4] Although extensive investigation usually seems unnecessary when hyaline bodies accompany visual field defects, some authors[2-4] have emphasized diagnostic discretion in these patients. The following report illustrates how an aneurysm of the ophthalmic artery might have been overlooked because of the presence of drusen in the optic nerve head.

## CASE REPORT

A 37-year-old woman had excellent health until May, 1967, when she began to have episodes of blurred vision with a "skim" over her eyes. In July, 1967, she experienced a period of complete amaurosis of the left eye, followed by a gradual return of diminished vision. During that episode, she was seen at another hospital and was told that she had optic atrophy and drusen of the optic nerve head. Her visual acuity progressively decreased, and she reported to Scott and White Clinic for the first time on November 28, 1967.

When she was first examined, visual acuity in the right eye was 20/20, and in the left, 20/70 with correction. The pupils were equal in size, but a Marcus Gunn pupillary response was noted in the left eye. Intraocular pressure was 14 mm Hg in each eye. The visual field examination of the left eye revealed a superior altitudinal defect with an arcuate scotoma extending inferiorly from the blind spot. The right eye had a relative superior arcuate scotoma (Fig. 1). Muscle balance and ocular rotations were normal. Numerous hyaline bodies were seen in both optic disks, and the left optic disk was moderately atrophic (Figs. 2 and 3). Spontaneous venous pulses were absent bilaterally. Hertel exophthalmometry was 12 mm Hg in both eyes. Retinal artery pressures were not recorded preoperatively.

The results of general medical and neurologic examinations were not remarkable. Kline, Kahn, and VDRL serologic tests were negative. The erythrocyte sedimentation rate (Wintrobe) was 30 mm in one hour, with a hemoglobin concentration of 13 g/100 ml. Glucose tolerance was within normal limits. An electroencephalogram and skull roentgenograms, including optic foramina views, did not demonstrate abnormalities. Percutaneous transfemoral selective left carotid angiography revealed a saccular aneurysm of the proximal portion of the left ophthalmic artery, beginning at the anterior aspect of the carotid siphon. The aneurysm had a wide mouth, a diameter of 4 mm, and was 10 mm in length (Fig. 4). A selective right carotid angiogram was interpreted as normal.

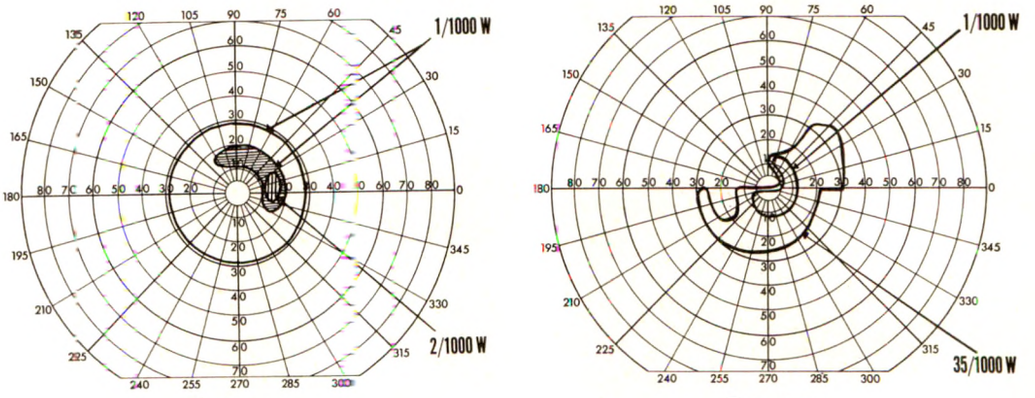
On December 4, 1967, a Silverstone clamp was applied and closed on the left internal carotid artery. Postoperatively, the only neurologic change was a transient blepharoptosis of the left eyelid. The clamp was removed on April 17, 1968. Ophthalmic examination on August 1, 1968, did not show progression of the visual field defects. The visual acuity in the right eye was 20/20, and in the left eye, 20/40-1. Ophthalmodynamometry revealed measurements of 76/28 mm Hg in the right eye and 16/5 mm Hg in the left eye. Intraocular pressure remained normal (14 mm Hg in each eye). The atrophy of the left disk was unchanged. A follow-up examination on February 5, 1970, did not reveal additional findings.

## COMMENTS

Aneurysms rarely occur in the ophthalmic artery—only 30 cases have been reported previously, and almost all of these lesions arose from the junction of the internal carotid and ophthalmic arteries. Most patients had visual field defects and decreased vision. The symptoms progressed slowly, and the course of the disease usually was benign.[5]

Drusen in the optic nerve head occur sporadically or in a heredofamilial, irregular dominant pattern based on an autosomal gene.[4,6] These hyaline excrescences have accompanied angioid streaks in pseudoxanthoma elasticum, corneal dystrophy, juvenile diabetes mellitus, Friedreich's ataxia, status dysraphicus, pituitary tumor, meningioma, and Wilson's disease.[4,6] They are also found in the atrophic optic nerves of patients with glaucoma, retinitis pigmentosa, and syphilis.[4] No other report of drusen in the optic nerve head in a patient with an aneurysm of the intracranial vessels was found.

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RIGHT EYE LEFT EYE

Fig. 1 (Cunningham and Sewell). Preoperative visual fields. Left eye demonstrates a dense superior altitudinal defect. There are bilateral arcuate scotomas.

Rucker,[1] and Chambers and Walsh,[7] have reported seeing patients with enlarged blind spots as we noted in our patient's right eye. These authors also described nerve fiber bundle defects such as in our patient's left eye. In these reports, the preponderance of peripheral contraction of the visual fields in the lower nasal portion was in contrast to the superior altitudinal defect noted in our patient. Although several reports show progression of visual field defects associated with drusen of the optic nerve head, opinions differ as to whether or not these hyaline bodies may cause decreased visual acuity. Stiefel and Smith,[2] in an excellent review of their cases, concluded that if central visual acuity is significantly reduced, as it was in our patient, careful neurologic and ophthalmic evaluation should be carried out before attributing the visual loss to the hyaline

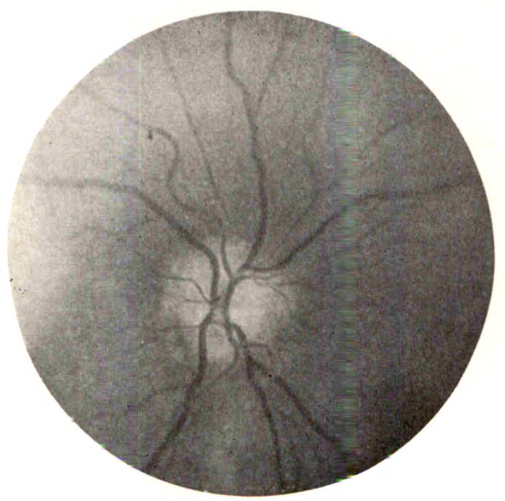


Fig. 2 (Cunningham and Sewell). Fundus (right eye) showing structural fullness of right disk and hyaline bodies of the optic nerve head.

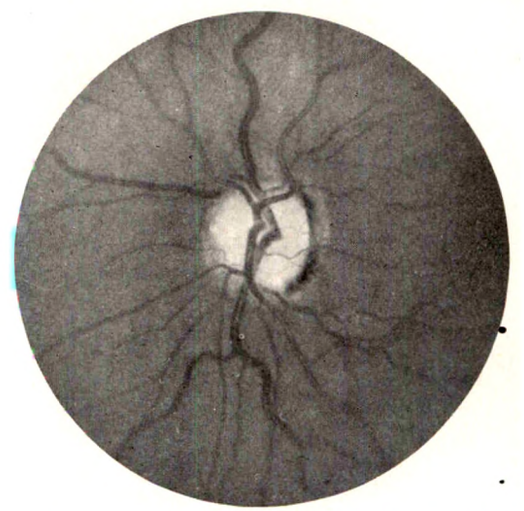


Fig. 3 (Cunningham and Sewell). Fundus (left eye) showing moderate optic atrophy and hyaline bodies of the optic nerve head.

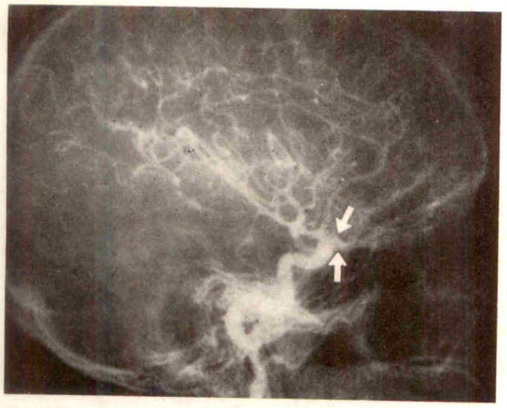


Fig. 4 (Cunningham and Sewell). Arteriogram (left carotid) demonstrating aneurysm of proximal portion of the left ophthalmic artery.

bodies alone. Optic atrophy without an obvious cause also warrants further clinical investigation.

## Summary

A 37-year-old woman with a significant decrease of visual function exhibited an aneurysm of the ophthalmic artery and drusen of the nerve head. To our knowledge, the coexistence of these conditions has not been reported previously.

Drusen usually do not cause abnormal pupillary responses and progressive loss of central acuity. Patients with such findings deserve careful ophthalmic and neurologic evaluation to screen out more serious underlying defects.

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# ACHROMATOPSIA IN PINGELAP ISLANDERS

## Study of a Genetic Isolate

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Patients with congenital achromatopsia (total color blindness, rod monochromatism) typically complain of poor visual acuity and aversion to bright lights, since these symptoms are produced by their widespread loss of functioning retinal cones.[1] The incidence of this unusual vision disturbance is much lower than the commonly occurring forms of sex-linked color deficiencies, and affects males and females in equal numbers. The high rate of ancestral consanguinity (31% in Europe and 75% in Japan) in pedigrees with affected members indicates that the mode of inheritance is autosomal recessive.[2] Holm and Lodberg,[3] in their study of seven generations, including about 300 people, all from a small island off the coast of Denmark, found 20 persons with achromatopsia. Pedigrees such as this permit the study of phenotypic variations as well as a great many known carriers with a view towarl detecting carrier signs.

For two weeks we studied a group of South Pacific Islanders, the Pingelapese, who, according to a preliminary survey,[4] showed a high incidence of a condition closely resembling achromatopsia. Fortunately, a large number of Pingelapese have emigrated to the island of Ponape, some 190 miles from Pingelap, where the availability of electricity and hospital facilities allowed thorough examination.

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### History

Pingelap atoll is located in the Eastern Caroline Islands which are part of the huge archipelago known as Micronesia. This three-million square mile area of the Pacific Ocean includes the Caroline, Marshall, and Mariana island groups, and since the end of World War II is known collectively as the Pacific Trust Territory of the United States. Over a period of 250 years, many nations, including Spain, England, Germany, Japan, and America have instituted cultural and social changes on these islands, but it was a natural catastrophe two centuries ago which brought about the high incidence of achromatopsia in the Pingelapese. In the late 18th century a typhoon of great intensity struck the tiny atoll. Deaths from injuries, disease, and starvation reduced the population from about 500 inhabitants to about 20 persons. The survivors lost little time in rebuilding and repopulating their community, and by the early 1900s they numbered several hundred. At this time, the (German) administrators of the district, to alleviate overcrowding on Pingelap, assigned more than 100 natives to the large island of Ponape. Many other Pingelapese followed these early migrants, and it is now estimated that there are about 900 on Ponape and 600 remaining in Pingelap. Although this island contains several groups of immigrant populations, each engages in endogamous marriage practices, so that even in contemporary times the Pingelapese maintain in their population a high frequency of the gene for achromatopsia. The original survey[4] showed that the incidence of affected persons in the Pingelap Island population was 6%. Using the Hardy-Weinberg formula,[5] the calculated incidence

of the carrier state in this group is 37%. In a general population, on the other hand, one out of 30,000 persons was reported to be affected with achromatopsia,[6] and only 1% are carriers for the disorder.

## Materials and methods

*Routine testing*—With the help of Peace Corps volunteers who were fluent in Pingelapese and local dialects, we were able to obtain histories and perform subjective testing. Every patient was tested on the standard Snellen eye chart or illiterate E test at a distance of 20 feet. For children and those adults with severely reduced vision, the flash-card vision test of the New York Association for the Blind was used at a distance of five feet. Refractions were performed on any whose acuity was less than 20/30. Direct and indirect ophthalmoscopy was routinely done on all patients after dilatation, and photographs were taken with a portable (Model PRV Olympus Corp.) fundus camera.

*Color vision*—The Ishihara and the Hardy-Rand-Rittler pseudoisochromatic tests were administered under standard illumination by placing a Macbeth Illuminant "C" filter in front of a 100 watt frosted tungsten bulb. Patients with color defects were further tested with the Farnsworth D-15 panel, and Sloan achromatopsia strips.

*Special testing*—Determination of final dark adapted thresholds and electroretinography (ERG) were performed on patients with unusual visual problems, those suspected of being achromatic, and those known to be achromatopsia carriers. The ERG was recorded using a slightly modified Cambridge Model VS III portable electrocardiograph machine. A small solid state amplifier allowed the "sync-out" pulse from the Grass PS-2 photostimulator to activate the marker pen whenever the flash tube was pulsed, thus obtaining a stimulus mark on the record. In addition, the response to low frequencies was reduced to eliminate pen drift by inserting an appropriate R-C network into the accessory jack receptacle. Electrical shielding of the patient was not necessary because the amplification system receives the ERG signal plus background, and returns the inverted common mode signal to the subject through the ground lead. This inverted "driven ground" signal, while allowing amplification of the differential signal, tends to eliminate in-phase activity such as AC hum. After mydriasis and anesthetization of the cornea, a Burian-Allen type contact lens electrode containing a drop of Isopto Alkaline, was placed on the patient's eye. Metal disk reference and ground electrodes were fixed to the forehead and wrist with saline paste. For optimum recording, it was important to thoroughly cleanse and slightly abrade the skin area to which electrodes were attached with alcohol-soaked gauze sponges.

Final dark-adapted thresholds were obtained with a small box containing a light source powered by the ophthalmoscope transformer, a camera shutter set at 1/25 second, removable neutral density filters, and a pair of polaroid plates which could be varied to obtain small changes in stimulus intensity. A small red fixation light ensured that the stimulus, which subtended an angle of about 4.5°, fell 15° temporal to the fovea. Typically, the patient would have his right eye dilated and securely patched for at least one-half hour before the test. During this period of dark adaptation the examiner would explain the nature of the test and demonstrate what would be required. There was little difficulty obtaining reliable data once the patient understood the task. The object of this test was simply to establish the sensitivity of the subject's retinal rods relative to normal subjects; therefore, final thresholds are listed as higher (+) or lower (−) than averaged normal values in log units (Table 1).

## Results

A brief summary of the findings for the 26 affected patients is given in Table 1. Without exception, the affected individuals

TABLE 1

SUMMARY OF FINDINGS IN PATIENTS WITH ACHROMATOPSIA

| Patient, Sex, and Age | Best Visual Acuity | Refractive Error | Fundus Appearance | ERG b-wave Amplitudes* | | | | Final Thresholds | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $S_{16}$ White (30/second) | $S_1$ Blue | $S_1$ White | $S_{16}$ White | | |
| 1. M-17 | 20/200<br>20/200 | −6.00<br>−8.25 | Myopic conus with tilted disks, normal vessels, macular granularity, diffuse foveal reflex | Absent | | | | −0.4D | Marked nystagmus, ceases on fixation |
| 2. F-48 | 20/200<br>20/200 | − 7.00<br>− 7.00 | Marked myopic dengeneration changes in posterior pole, choroidal thinning of retina with several areas of peripheral lattice degeneration, some narrowing of arterioles | Absent | 85 | 120 | 150 | — | No nystagmus |
| 3. M-43 | 10/100<br>10/200 | − 5.00<br>− 5.00 | Round demarcated pigmented macular lesions RE>LE, thinning in posterior pole, large pigmented temporal crescents in both eyes | Absent | 135 | 160 | 205 | — | Macular lesions represent probable congenital toxoplasmosis, no nystagmus |
| 4. M-25 | 10/100<br>10/100 | − 8.00<br>− 7.00 | Myopic conus with tesselation of posterior pole, vessels and disks normal, macular areas granular diffuse foveal reflex | Absent | 100 | 110 | 170 | −1.0D | Moderate nystagmus, marked photophobia |
| 5. F-21 | 20/100<br>20/200 | − 0.50<br>− 0.50 | Normal disks, vessels, maculas | Absent | 240 | 290 | 375 | — | Very slight nystagmus |
| 6. F-21 | 20/70<br>20/100 | −12.50<br>− 9.00 | Large myopic crescents with nasal shift of vessels, thinning of retina with normal macular pigment | Absent | 50 | 100 | 195 | +0.7D | Pseudoptosis, jerky nystagmus in primary position |
| 7. F-46 | CF 3 feet<br>CF 3 feet | About<br>−15.00 | Atrophic disks which have irregular mottled lesions confluent with round atrophic lesions of maculas, vessels slightly narrowed, periphery normal, patient has eccentric fixation | Absent | nil | 85 | 120 | +1.5D | Superior arcus in both eyes, wandering slow nystagmus with jerky end position nystagmus |
| 8. M-27 | 20/100<br>20/100 | −13.50<br>−13.50 | Disks and vessels normal, inferotemporal myopic crescent with some shift of vessels, tigroid fundus | Absent | 155 | 210 | 255 | +1.0D | Rapid jerky nystagmus |
| 9. M-6 | 5/50<br>5/70 | Emmetropic | Normal disks, vessels, maculas | Absent | 155 | 195 | 210 | — | Rapid nystagmus increasing in lateral fields of gaze |
| 10. M-61 | CF 4 feet<br>CF 4 feet | Emmetropic | Severe peripapillary choroidal sclerosis, bone corpuscle and clump pigmentation, normal disks, arterioles show marked A-V crossing, heavy lattice changes in periphery, vitreous has many floaters | Absent | 35 | 60 | 70 | — | No nystagmus |
| 11. F-21 | CF 5 feet<br>CF 5 feet | −10.00<br>−10.00 | Large myopic crescents with heavy pigmentation, irregular atrophic areas in both maculas | — | — | — | — | | Marked nystagmus |
| 12. M-18 | 8/200<br>8/200 | − 9.50<br>−11.50 | Normal disks with large pigmented crescents, macular areas normal, diffuse foveal reflex | — | — | — | — | — | Nystagmus |
| 13. F-21 | 20/200<br>20/200 | − 6.00<br>− 6.00 | Pigmented temporal crescents, marked choroidal pattern over posterior pole, diffuse foveal reflex | — | — | — | — | — | Nystagmus |

* Normal (minimum) b-wave amplitudes for these stimuli are: $S_1$ blue = 160, $S_1$ white = 200, $S_{16}$ white = 330$\mu$V; minus sign = below normal threshold, plus sign = above normal threshold in optical density units.

TABLE 1 (*Continued*)

| Patient, Sex, and Age | Best Visual Acuity | Refractive Error | Fundus Appearance | ERG b-wave Amplitudes* | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $S_{16}$ White (30/second) | $S_1$ Blue | $S_1$ White | $S_{16}$ White | Final Thresholds | |
| 14. F-19 | 16/200<br>18/200 | −12.00<br>−11.00 | Disks tilted, large heavily pigmented temporal crescents, thinning of entire posterior pole, maculas have round atrophic areas with a slight tapetal reflex | — | — | — | — | — | Nystagmus |
| 15. F-19 | 3/200<br>2/200 | −16.00<br>−16.50 | Tilted disks with a large choroidal pigment ring, thinning of entire posterior pole | — | — | — | — | — | Moderate nystagmus |
| 16. F-13 | 3/200<br>3/200 | −10.00<br>− 9.00 | Slight tilting of disks with temporal crescents, maculas normal with good foveal reflexes | — | — | — | — | — | Nystagmus |
| 17. M-15 | 20/200<br>20/200 | − 2.50<br>− 3.00 | Normal disks, vessels, and macula | — | — | — | — | — | Rapid nystagmus |
| 18. F-16 | 15/200<br>15/200 | −14.00<br>−14.00 | Large myopic crescents with shift of vessels, tigroid fundus, good foveal reflexes | — | — | — | — | — | Questionable nystagmus |
| 19. M-10 | 15/200<br>15/200 | − 1.00<br>− 1.00 | Small pigment crescent next to disk, tigroid area below right disk, disks, vessels and maculas normal | — | — | — | — | — | Nystagmus |
| 20. M-6 | — | Emmetropic | Normal disks, vessels, maculas, good foveal reflex | — | — | — | — | — | Marked nystagmus |
| 21. F-13 | 20/70<br>20/70 | −12.00<br>−11.50 | Disks tilted with vessel shift, marked temporal crescents, atrophic macular areas with golden sheen, good foveal reflex | — | — | — | — | — | Severe nystagmus, increasing in tertiary positions of gaze |
| 22. F-8 | 5/70<br>5/70 | − 4.00<br>− 4.50 | Disk and vessels normal, thinning inferiorly, atrophic areas in maculas with tapetal reflex | — | — | — | — | — | Nystagmus |
| 23. M-37 | 20/150<br>20/150 | − 6.50<br>− 7.50 | Inferotemporal crescents, vessels normal, irregular atrophic areas in maculas with tapetal reflex, choroidal pattern inferior to disks | — | — | — | — | — | Slight fixation nystagmus in secondary and tertiary positions of gaze |
| 24. M-43 | 12/100<br>12/200 | − 2.75<br>− 2.75 | Disks normal, very large pigmented inferotemporal crescents, tigroid pattern in posterior pole, no foveal reflex | Absent | 160 | 170 | 230 | +0.2D | No nystagmus, arcus senilis in both eyes |
| 25. M-18 | 14/200<br>14/200 | − 0.50<br>− 1.00 | Normal disks, vessels, maculas | Absent | 200 | 280 | 325 | +0.4D | No nystagmus in primary position, marked jerky nystagmus in secondary and tertiary positions |
| 26. M-20 | 20/200<br>20/200 | − 3.00<br>− 2.75 | Disks normal, irregular atrophic area in maculas | Absent | 170 | 190 | 230 | +0.2D | Marked nystagmus |

had absent color vision and a best corrected acuity of 20/70 or less. In 13 patients on whom ERGs were done, there was an extinguished response to an intense 30 cps flickering light, a finding indicating that cone function in these patients was severely impaired. Normal rod function is, of course, as much a sine qua non of achromatopsia as generalized cone malfunction, and the results of several other tests must be scrutinized before a definitive diagnosis can be made.

Qualitatively, the results of the Farnsworth D-15 panel demonstrated that the scotopic system in these patients subserves vi-

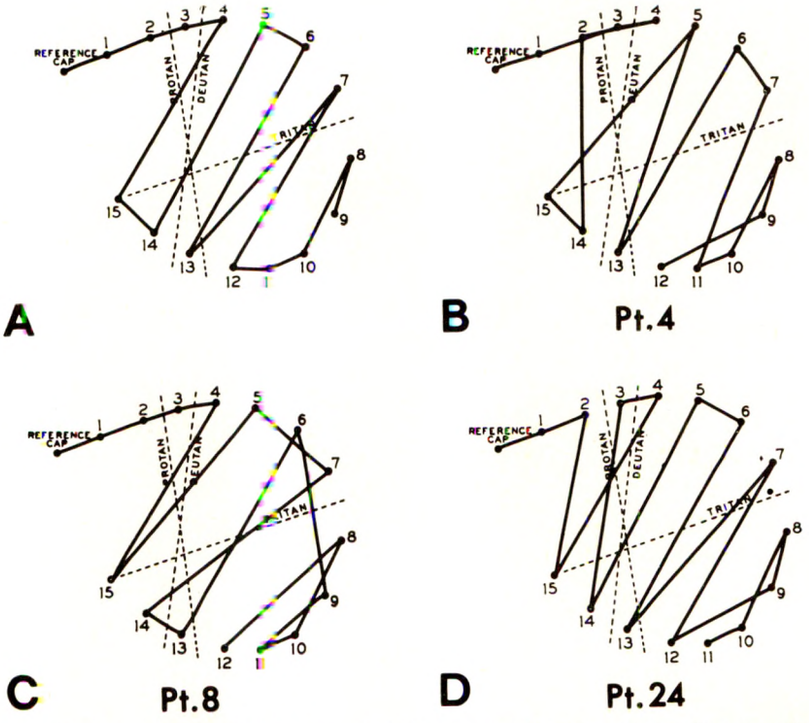



Fig. 1 (Carr, Morton, and Siegel). Farnsworth D-15 panel test results. If the disks are aligned on the basis of their scotopic brightness values, pattern A is obtained. It is clear that the achromatic patients Nos. 4 (B), 8 (C), and 24 (D), whose patterns were typical, use rod vision even at moderately bright light levels.

sion even at moderately bright light levels. Figure 1-A shows how the colored disks would be ordered on the basis of their scotopic brightness as computed by Sloan.[7] For comparison, actual patterns made by three affected patients are shown in Figure 1-B, C, and D. The test patterns of the different patients are remarkably similar and their approximation to the scotopic arrangement unmistakeable.

Two other tests of great importance in this regard are the dark-adapted (scotopic) ERG, which gives information about the massed electrical response of millions of rods, and the more sensitive test of dark adaptation. Ideally, the latter procedure should include the measuring of thresholds in several areas of the retina; however, our portable device allowed only measures of the final absolute threshold (not rate of adaptation) in one area of the retina. The results of both these tests are abnormal for the majority of affected patients (Table 1). But before advancing the notion that both cones *and* rods were affected, it should be noted that the majority of these 26 patients are myopic. Sixteen of them (62%) range from −5.00 to −16.50 diopters and all show pronounced fundus changes commonly associated with myopia. For the sake of brevity, refractive errors in Table 1 are given as spherical reductions; few of the patients had astigmatic errors greater than about two diopters, and none higher than 3.50 diopters. Including all degrees of myopia, it is seen that about 80% of the affected subjects have both achromatopsia and nearsightedness. It was precisely the highly myopic patients who showed low amplitude ERGs and raised (+) final thresholds, whereas emmetropic or mildly myopic patients (e.g., Patients 5, 9, 24, 25, and 26) gave normal responses to the low intensity

($S_1$blue) flash, the stimulus usually used to demonstrate rod function. Higher intensity flashes would be expected to be lower than normal since they also elicit a cone contribution to the response which of course would be lacking in these patients.

Figure 2 shows ERG recordings of a normal subject, one with six diopters of myopia, a patient (No. 25) who is affected but nearly emmetropic, and a patient (No. 4) who has both achromatopsia and high myopia. Clearly, the myopic patients have reduced b-waves, and the myopic patients with achromatopsia have the lowest responses of the whole group. It is not expected, however, that myopia itself invariably produces decreased ERGs since Franceschetti and associates[8] have shown that although b-waves from the affected eyes of patients who are unilateral myopic are very often much lower than their normal fellow eye, exceptions are not unusual (e.g., our Patient 8). Although high myopia affects rod function (which in uncomplicated achromatopsia is normal) a clear distinction can be made on the basis of ERG responses, final thresholds,

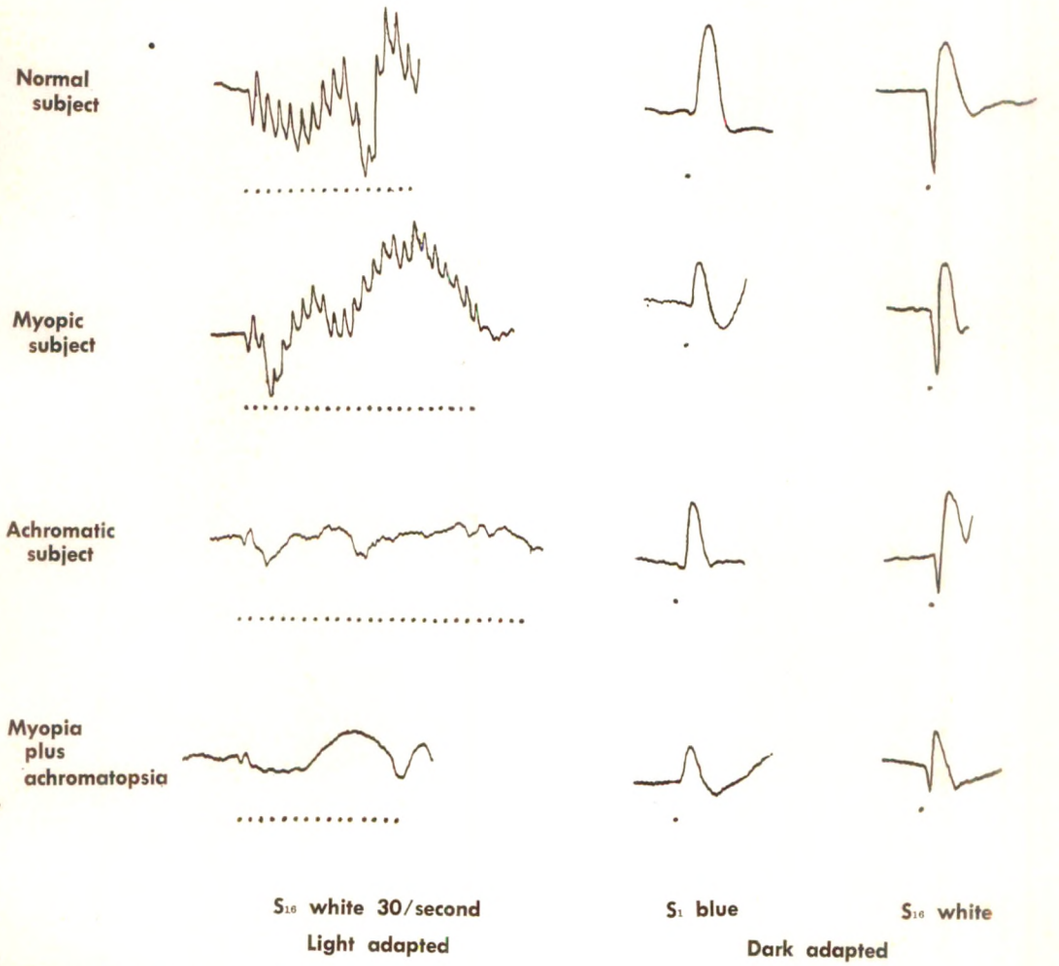



Fig. 2 (Carr, Morton, and Siegel). ERG tracings obtained using the equipment described in the text. The stimuli values $S_1$ and $S_{16}$ refer to the weakest and most intense flashes produced by the photostimulator. To produce maximal rod responses the eye was dark adapted for 10 minutes and then the low intensity $S_1$ flash with a (Grass Co.) blue filter was used.

and fundus appearance, between this group with myopia-achromatopsia and certain forms of generalized retinal degenerations in which symptoms relating to the cone impairment predominate, (e.g., the group III cone-rod dysfunction of Goodman and associates[9]).

Most of the affected patients had nystagmus. This is a variable finding in achromatopsia, however, and can range (as Table 1 shows) from no visible nystagmus to marked movement. There appears to be little relation between degree of nystagmus and any other finding.

Photophobia, or more accurately in the case of achromatopsia, aversion to light, was present to some degree in all of the affected patients. Several patients wore (plano) sunglasses, but the majority preferred not to, though it was obvious that they avoided open sunlight and continually looked downward to prevent dazzling.

Most completely achromatic subjects show lack of foveal reflex and the macular region often has a granular appearance.[9] Many of those affected showed macular abnormalities, and those having high myopia also showed fundus pathology associated with that disorder. Several patients had retinal changes that were independent of the achromatopsia and myopia. For example, Patient 10 had severe peripapillary choroidal sclerosis, generalized retinal pigmentation, and heavy lattice degeneration in the periphery. The very low scotopic ERG amplitudes in this patient reflected the extensive retinal pathology. Patient 3 presented lesions that appeared to be the result of congenital toxoplasmosis.

Ocular examinations were performed on 24 known carriers (i.e., persons who had one affected parent or women who had affected children). Of these, all but one older patient had a corrected acuity of at least 20/30 and many could read the 20/15 line with ease. Color vision as tested with the Ishihara and H-R-R plates was normal in all these patients. Electroretinography performed on several carriers showed, with the exception of the one patient noted below, completely normal photopic and scotopic responses.

Ophthalmoscopic examination revealed a variety of retinal changes, most of which are found in the general population as a result of aging. Of particular note was the finding of angioid streaks in three of the older carriers. In two patients this was associated with reduced vision and macular degeneration. These latter changes were, however, more typical of the senile form of macular dystrophy. About a third of the carriers show Gunn's dots[10] (hyaline verrucosities of the internal limiting membrane), which gave a pinpoint refractile appearance in the peripapillary area. Due to the superficial nature of these tiny nodules and their common occurrence in otherwise normal eyes, no significance can be attributed to them.

Of the younger carriers, one subject (No. 46) showed very marked fundus pathology, apparently of a vascular nature. Both eyes demonstrated extensive venous sheathing and several atrophic areas throughout the peripheral retina; the central areas appeared granular but otherwise normal. We were completely unprepared, therefore, to find a virtually extinguished ERG response to the flicker stimulus. This woman's photopic and scotopic ERG records are presented in Figure 3 along with responses from another normal carrier of about the same age for comparison. The scotopic ERG amplitudes were also smaller in Subject 46 than that of the other carriers, but this could have been due either to her extensive retinal changes or simply to the loss of the cone contribution to these responses, as in achromatic individuals. Of particular interest here is the fact that in spite of this marked cone dysfunction, visual acuity and color vision were normal in this woman. Obviously, the foveal cones were spared, since the small number of receptors in that region (1 or 2% of all the cones in the retina), while contributing little to the photopic ERG response, could nonetheless remain completely normal. But it is the generalized loss of cone function in this known carrier of achromatopsia that holds our at-

tention. Can her defect be considered a "carrier sign" of the disorder? This appears unlikely, since many of the other carriers who were tested had normal flicker ERGs. Moreover, this patient had obvious fundus pathology, which strongly suggests that the selective impairment of the cone system was a *secondary* involvement. This patient's functional findings are remarkably similar to Siegel and Smith's[11] Patient A with acquired achromatopsia, a 33-year-old woman whose visual acuity and color vision were only mildly affected, but in whom there was massive loss of cone activity as evidenced by an extinguished flicker ERG and gross constriction of her color (naming) fields. Interestingly, our patient evinced no photophobia, whereas a severe "dazzle effect" was a pronounced feature of Siegel and Smith's case. However, the presence of some functioning cones in this patient, as evidenced by a small photopic response (observable in the ERG record from the right eye) perhaps accounts for her lack of discomfort in bright lights. Because of the ophthalmoscopically visible pathology, we examined the medical background of our unusual carrier. She gave birth to her three children at the hospital, but the delivery and postpartum course in each case was uneventful. There was no indication of her having a systemic disease serious enough for hospitalization or intensive treatment during the 10-year period covered in the record. Specific tests done at the time of each admission included Kahn, sputum for AFB, CBC, urinalysis, and chest x-ray studies. These were normal or negative.

## Discussion

Pedigree analysis of the Pingelap population with regard to several genetic traits is in preparation and indicates that in so far as

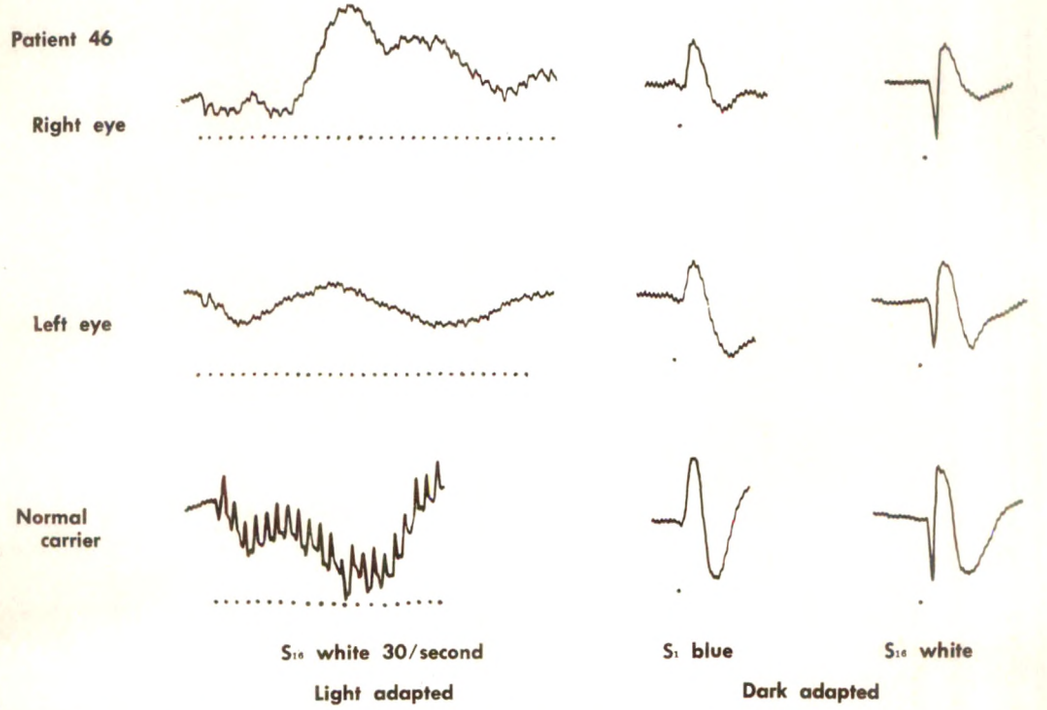



Fig. 3 (Carr, Morton, and Siegel). ERG recordings from the right and left eyes of Patient 46, a carrier with fundus pathology, predominantly of vascular origin, but who had good acuity and normal color vision. The reduction of cone function is most marked in the left eye, while rod responses in both eyes are within the lower limits of normal. Another carrier (Patient 48) is presented for comparison.

the ocular disorder is concerned, the mode of transmission is autosomal recessive. Typically, affected offspring had unaffected parents, who themselves had parents with achromatopsia or who had affected siblings. Usually, consanguinity of some degree between parents of affected children could be proven.

One of the outstanding features of our achromatic population is the large percentage of associated high myopia. This was not noted by Holm and Lodberg,[3] in the literature review by François and associates,[12] or in the 50 patients representing complete and incomplete forms of the syndrome studied by Goodman and his colleagues.[9] We are therefore reluctant to assume that high myopia is an effect of the gene for achromatopsia, although this possibility cannot be excluded. There seems little doubt that high degrees of myopia are transmitted as an autosomal recessive,[13] and if these genes are present in a highly inbred population such as the Pingelapese, the incidence should be much greater than in the general population.

It is of interest to pursue this relationship between achromatopsia and myopia in this group. Any discussion of the genetic probabilities must be theoretical, however, since matings between affected individuals never occur in this population. Thus, it is impossible to know the answers to such questions as: (1) Did matings of two affected individuals with both high myopia and achromatopsia ever produce an offspring with only achromatopsia? or, (2) Did matings of two affected individuals with only total color blindness ever result in an offspring with both disorders? The extensive pedigree analyses made during this trip and an earlier one show no instances of mating between affected individuals and in all cases there is a strict autosomal recessive pattern of heredity.

There is strong evidence against the gene loci for achromatopsia and myopia being on different pairs of chromosomes. Such an arrangement would result (according to the Mendelian law of independent assortment) in the following: Double heterozygotic parents (i.e., those carrying single genes for each of the conditions) could have 9/16 offspring who were phenotypically normal, 3/16 offspring with achromatopsia, 3/16 who were myopic, and 1/16 having both myopia and achromatopsia. The actual incidence of the different types is far from this prediction, making the possibility of independent gene action very unlikely. A more probable explanation is that the gene loci for myopia and achromatopsia exist as a linked pair on one chromosome. This pair of linked genes could have two configurations in the double heterozygote: (1) coupled (Fig. 4-left), in which both recessive alleles are on the same chromosome; or (2) in repulsion (Fig. 4-right), where the deleterious genes (a and m) are on opposite chromosomes. Two parents of the genotype shown in Figure 4-left can have normal and doubly affected (myopic and achromatic) children in the ratio 3/4:1/4 as shown in Figure 5-top. Two parents with the deleterious genes in repulsion (Fig. 4-right) can have myopic, normal, or achromatic children in the proportions 1/4:2/4:1/4, but *no* doubly affected children. Therefore, the coupled gene arrangement serves to explain most of the association between the two disorders. However, to completely account for the presence of those individuals

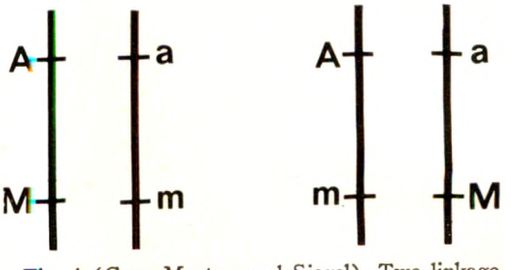



Fig. 4 (Carr, Morton, and Siegel). Two linkage arrangements of the achromatopsia gene (a) and the myopia gene (m) in the double heterozygote. The genes could be coupled (i.e., on the same chromosome) as on the left, or in repulsion, shown on the right. Parents of the genotype shown at the left can have normal children or children who have linked genes in repulsion. Parents of the genotype shown at the right can have normal children, achromatic children, or myopic children.

who were achromatic with no significant degree of myopia, recombination or crossing over, a process whereby material is reciprocally exchanged between members of a chromosome pair must be considered.

The further apart two gene loci are on a chromosome pair, the greater the likelihood of an exchange occurring. If the genes are very far apart and recombination occurs as much as 50% of the time, the number of gametic types produced will not be distinguishable from two genes located on different chromosome pairs which can assort independently during meiosis. For the chromosome pair shown in Figure 5-top, the possible offspring are a homozygote normal, two carriers, and a doubly affected child. If chromosome breakage and recombination occurs between the two genes in one or both parents, it is possible to produce new genotypes: achromatic *or* myopic individuals (Fig. 5-bottom) in addition to the non-recombinative forms. The schema of recombinative genotypes also shows that there is just as much chance of uncomplicated high myopia occurring as achromatopsia without myopia. We did not find any "pure" high myopia among any of the subjects examined, although only about a third of all the affected individuals noted in the original survey were seen.

Since poor vision was the only criterion used in selecting the majority of our subjects, our selection of patient material was not biased in favor of those having both conditions. Many of the children on whom subjective testing could not be done, and the several hundred natives living on the island of Pingelap, where lack of electricity made detailed testing difficult, were in a sense excluded from consideration, and perhaps further investigation of these persons will reveal some with high myopia. Absence of "pure" high myopia in this population would argue strongly against two linked genes with a detectable recombination rate. Since high myopia is not produced by the gene for achromatopsia in other populations, and evidence of recombination between the two

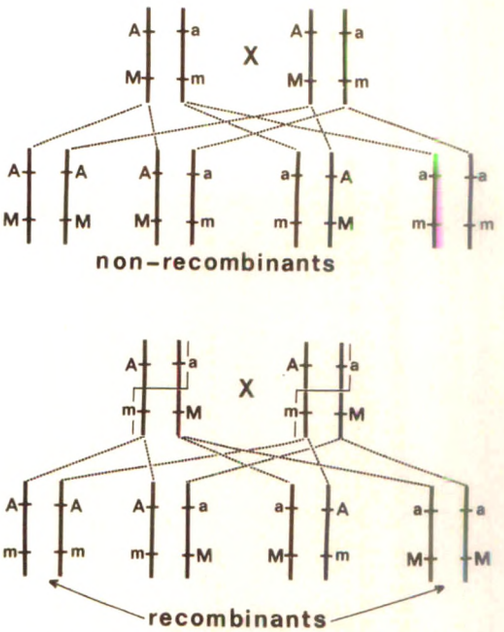



Fig. 5 (Carr, Morton, and Siegel). Possible offspring of double heterozygotes, where the genes are coupled on the same chromosome, are shown in the top figure. The affected offspring are both achromatic and myopic. All others have at least one normal allele (A and M) to produce a normal individual. If the exchange of chromosomal material takes place between the two gene loci as shown in the lower figure, offspring may be achromatic or myopic.

genes is incomplete, what other mechanisms would account for the close association of these defects among the Pingelapese? One possibility is a single mutational event (such as an inversion, unequal crossover, or deletion) which simultaneously affects two linked genes. Then the probability of recombination could be negligible, and we would not expect to find "pure" high myopia. Unfortunately, this hypothesis is not distinguishable by genetic evidence from a pleiotropic effect of the allele for achromatopsia, and also leaves unexplained the several achromatic individuals without appreciable refractive error.

The Pingelap Islanders are not an exceptional genetic isolate; many have been reported from remote areas and no doubt several more with other ocular problems will be

discovered. The combination of swift transportation and portable diagnostic equipment afford the ophthalmologist a unique opportunity to study in detail great numbers of patients afflicted with rare disorders. It is now possible to obtain, in a short period of time, enough information to completely define mode of transmission, expressivity, and penetrance of a specific genetic abnormality.

## Summary

A high percentage of a genetically isolated population from the island of Pingelap was found to have symptoms of poor visual acuity, loss of color vision, nystagmus, and photophobia. History indicated a high degree of ancestral consanguinity, and study of family groups showed the disorder to be transmitted as an autosomal recessive trait. Ocular examination, including psychophysical testing as well as electroretinography, was performed on affected patients and known carriers and revealed the disease to be congenital achromatopsia. This condition, relatively rare in the general population, was present in 6% of these islanders. In addition, about 80% of the affected individuals had associated myopia, the majority in the pathologic range.

### Acknowledgments

We thank Dr. Irene E. Hussels, who performed the original visual screening of the Pingelap population, and Jane Hurd and Beth Rye, Peace Corps volunteers, for their service as translators and their invaluable assistance. We also thank Dr. E. Pretrick, of Kolonia Hospital, who provided space for the study and arranged for transportation of the patients and ourselves on the island of Ponape.

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# PERIODIC ALTERNATING NYSTAGMUS

## A Report of Eight Cases

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Periodic alternating nystagmus is infrequently recognized in this country. Towle[1] counted only 40 cases in the world literature, and of these, but three were in English. Only one case has appeared in the American ophthalmic literature.[2] The following is a report of eight cases of periodic alternating nystagmus, a description of its characteristic nature, and an etiologic differential diagnosis.

### Case reports

*Case* 1—This 38-year-old black woman was hospitalized because of leiomyomata of the uterus. Neuro-ophthalmic consultation was requested because of abnormal eye movements. On ocular examination the corrected visual acuity was 20/25 in both eyes. The pupils reacted 2+ to light, and there was a 4+ reaction to near. The slit lamp, fundus, and visual field findings were normal.

Motility examination revealed classic periodic alternating nystagmus. This was manifested by a horizontal, jerk-type nystagmus whose amplitude gradually increased to a maximum, and then similarly abated. This phase lasted 110 seconds and was followed by a 20-second quiet interlude during which there was no nystagmus. A similar sequence then followed with the rapid phase in the opposite direction. The amplitude of the oscillations increased when she looked into the direction of the rapid phase, and decreased when she looked into the direction of the slow phase. This cycle repeated itself over and over again. Of interest was the fact that the horizontal nystagmic movements were also present in vertical gaze. During the height of the oscillations the patient's visual acuity decreased and she experienced oscillopsia.

The past history revealed that at the age of 16 years she had delivered a stillborn fetus and several months later a serological test for syphilis was reactive. She was treated for this with penicillin at age 16 and again at age 20. At the age of 30 years a progressive neurologic disease began which was unremitting. In 1961 she began to note aching pains in her legs and began having difficulty seeing. An optician told her she had "jumping eyes." There was an insidious onset of difficulty in walking and paresthesia in the extremities. Hearing loss began on the left. She was hospitalized in 1963 and thought to have multiple sclerosis. By 1967 she required a walker, and began having difficulty with bladder and bowel control. One year prior to admission she obtained a wheelchair.

Neurologic examination revealed motor weakness in the lower extremities, and a mild dystaxia of the upper extremities. Skull x-ray examination and a cervical myelogram were normal. Blood tests for syphilis revealed a weakly reactive VDRL and a 2+ reactive FTA-ABS test.

### Comment

This 39-year-old woman had a stillborn fetus at the age of 16 years, and shortly thereafter was found to have a reactive serological test for syphilis. She was treated for this with penicillin at the ages of 16 and 20 years. In the past 10 years she developed progressive spastic paraplegia and periodic alternating nystagmus. She also had lightning pains in the right upper extremity, involvement of sphincters, and a hearing loss in the left ear. The impression was neurosyphilis with myelitis and periodic alternating nystagmus. A three-month course of ampicillin and probenecid (Benemid) was advised.

*Case* 2—A 49-year-old white man was referred with a chief complaint of "attacks of blurred vision." At the age of 44 years he noted the onset of episodes of blurred vision and oscillopsia which would last for five to 30 seconds. These increased in frequency to approximately 100 a day. The patient also noted clumsiness in walking and slurring of his speech for the past 18 months. Three years previously neurologic examination, lumbar puncture, bilateral carotid and right vertebral arteriograms were normal. A trial of corticosteroids was of no help.

On examination the visual acuity in the right eye was 20/25 and in the left eye 20/30. The visual fields and ocular fundi were normal. Electronystagmography demonstrated periodic alternating nystagmus with rapid phase to the right followed by a nystagmus with the rapid phase to the left. When

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TABLE 1

ELECTRONYSTAGMOGRAPHIC DATA FROM CASE 2

| | Rapid Phase to the Right | | | Rapid Phase to the Left | | |
|---|---|---|---|---|---|---|
| | Right Gaze | Primary Gaze | Left Gaze | Right Gaze | Primary Gaze | Left Gaze |
| Duration (seconds) | 134 | 111 | 81 | 91 | 108 | 113 |
| Frequency/second | 3 | 3 | 1.8 | 1.8 | 2.2 | 4 |

the rapid phase was to the right, in right gaze the duration of the nystagmus lasted 134 seconds with an oscillation of three beats per second, in primary gaze the nystagmus persisted at 111 seconds at three beats per second, and in left gaze persisted for 81 seconds, at a rate of 1.8 beats per second. When the fast phase of the nystagmus was to the left, in right gaze the direction of each episode of nystagmus was 91 seconds with a frequency of 1.8 per second, and in primary gaze the duration was 108 seconds with a frequency of 2.2 per second, and in left gaze the duration was 113 seconds with a frequency of 4 per second (Table 1).

Optokinetic responses had no effect on the nystagmus in any direction. However, cold caloric responses had a definite effect in that irrigation of the ear with ice water abolished the nystagmus and reversed its direction.

Neurologic examination revealed mild dysarthria, vertical ocular dysmetria, modest abnormality in heel-to-shin testing, some imbalance in walking heel-to-toe, and some dyssynergy on foot patting and pivoting.

Skull x-ray films, electroencephalogram, serum FTA-ABS test, and spinal fluid examination were normal.

A trial of meclizine HCl (Antivert), isoxsuprine HCl (Vasodilan), and carbamazepine (Tegretol) showed no improvement. Diphenylhydantoin sodium (Dilantin) decreased the duration of the cycle by 30 seconds with a slight slowing of oscillations in the rapid phase to the left and a shorter period of crescendo in the rapid phase to the right. A repeat examination two years later revealed no change.

The clinical impression was periodic alternating nystagmus probably due to demyelinizing disease.

*Case 3*—A 21-year-old black woman was hospitalized with the chief complaint of headaches, nausea, and vomiting of 10 days' duration. Three days prior to admission she noted blurred vision and horizontal diplopia. Two days before admission severe vertigo and a staggering gait developed. This patient had sickle cell anemia since the age of three years requiring numerous transfusions, and had suffered bouts of abdominal and joint pain.

On admission she was lethargic and markedly ataxic. Spinal fluid examination revealed a normal opening pressure but a pleocytosis of 330 leukocytes/ml$^3$, 15% polymorphonuclear leukocytes, 85% mononuclear leukocytes, and a protein of 77 mg%. The impression was viral encephalitis and sickle cell anemia.

On neuro-ophthalmic examination the visual acuity was 20/60 in both eyes. There was a left blepharoptosis, a slight left hypertropia, and anisocoria, with the left pupil slightly larger than the right. Both pupils reacted well to light but there was a slight Marcus Gunn pupil phenomenon on the left. The optokinetic responses were right 1+, left 1+, up 3+, and down nil. The fundi showed slight optic nerve pallor on the left.

The most striking eye finding was periodic alternating nystagmus. An electronystagmogram showed disorganized, short, rapid saccades rather than a well-organized nystagmus. The periodic alternating nystagmus appeared as follows: left-beating nystagmus was 75 seconds per cycle at 28 to 35 beats per 10 seconds. There was a 10 to 15 second rest period, followed by a right-beating nystagmus of 110 seconds per cycle with 35 to 40 beats every 10 seconds. The left-beating nystagmus could be virtually eliminated by extreme right gaze, and the right-beating nystagmus could be reduced, though not eliminated, by extreme left gaze. The nystagmus could be increased by stimulating the visual attention, and diminished by having the patient stare at a blank wall. The nystagmus continued with the eyes closed. The nystagmus could be modified by the optokinetic drum, although not eliminated or reversed. The direction of the rapid phase could be reversed by irrigation of the left ear with cold water (30°C) during the left-beating nystagmus, and during right-beating nystagmus the rapid phase could be reversed to left-beating nystagmus by a similar irrigation into the right ear.

The patient was treated with whole blood for the hematologic problem, and the spinal fluid cleared in the succeeding three weeks. There was a gradual improvement in the patient's severe truncal ataxia. A 10-day course of corticosteroids gave no improvement.

The impression was postinfectious or viral meningoencephalitis with periodic alternating nystagmus and sickle cell disease with aplastic crisis.

*Case 4*—A 70-year-old white man complained of "a hemorrhage in the back of my left eye." Seven years previously the patient suffered a vitreous hemorrhage in the right eye with a permanent loss of vision. Tow months previously he noted a loss of vision in the left eye. A general medical examina-

TABLE 3

CLINICAL IMPRESSION IN EIGHT CASES OF PERIODIC ALTERNATING NYSTAGMUS

1. Syphilitic myelitis
2. Demyelinizing disease with cerebellar involvement
3. Encephalitis with cerebellar involvement
4. Total amaurosis secondary to vitreous hemorrhage
5. Total amaurosis secondary to syphilitic optic atrophy
6. Congenital
7. Encephalomyelitis
8. Congenital, associated with albinism

amaurosis. Case 5 had bilateral syphilitic optic atrophy, whereas Case 4 developed periodic alternating nystagmus two to three weeks following a vitreous hemorrhage. Cases 1 and 5 both had syphilis. Cases 6 and 8 should be considered congenital.

Case 8 was remarkable since the patient was a universal albino, but without the usual searching nystagmus seen characteristically in such individuals. There is no previous record in the literature of periodic alternating nystagmus associated with albinism.

The pathophysiology of periodic alternating nystagmus has not been firmly established. Duke-Elder[3] stated that the phenomenon was most probably a central vestibular disturbance but that the mechanism was not clear. Kestenbaum[9] also indicated a central vestibular mechanism as the cause of this form of nystagmus. Kornhuber[19] proposed a central vestibular disturbance following a lesion in the tegmentum. He stated that the nystagmus was caused by a bilateral lesion of parts of the rostral paramedian reticular formation of the pontomesencephalic tegmentum.

Towle[1] reported the first case of periodic alternating nystagmus studied neuropathologically and found an arachnoid cyst caudal to the cerebellum, displacing the cerebellum upward, with medullary compression. His second case[24] studied neuropathologically was found to hae a midline posterior fossa (Arnold-Chiari variant) lesion. These two cases have strengthened the hypothesis that a central vestibular disturbance is present in periodic alternating nystagmus. The fact that periodic alternating nystagmus may occur on a congenital basis as well as following blindness due to ocular disease does not necessarily rule out the presence of a concomitant central vestibular lesion.

It is our feeling that periodic alternating nystagmus is not as rare as it has been previously reported. Because of its characteristic nature it can be easily recognized merely by studying all cases of nystagmus over a more prolonged period of time than is usual, and comparing right and left lateral gaze on repeated occasions. Three of our eight cases have been recognized in the past six months.

It is important to recognize this peculiar form of nystagmus because of its known etiologic factors. These include demyelinizing disease, neurosyphilis, encephalitis, blindness, congenital anomaly, and albinism. Their recognition may often obviate the necessity for extensive neurologic studies.

A careful history should be taken, inquiring as to onset, exacerbations, and remissions. A complete ophthalmic and neurologic examination, including examination of the serum FTA-ABS test and spinal fluid are suggested as the initial workup in these cases.

## SUMMARY

Periodic alternating nystagmus is a characteristic neuro-ophthalmic motility disturbance. Horizontal nystagmus with the rapid phase to the right is followed periodically by left-beating nystagmus. This pattern recurs at regular intervals. This entity is present in vertical gaze, and is an exception to the general rule that horizontal nystagmus on upgaze or downgaze points to congenital nystagmus. Periodic alternating nystagmus is associated with certain clinical conditions; it is important to recognize this peculiar form of nystagmus because known etiologic factors include demyelinizing disease, neurosyphilis, encephalitis, blindness, congenital anomaly,

and albinism. Diphenylhydantoin sodium (Dilantin) therapy merits further trials in reducing oscillopsia in this disorder.

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grees of dysfunction of intraocular postganglionic innervation.

Abnormalities on pupillography were typical of defective oculosympathetic innervation with anisocoria, absent psychosensory response, and characteristic alterations of the pupillary reactivity (Fig. 1). The initial anisocoria average approximately 10.06 mm, and there was no significant difference in anisocoria between darkness and dim background light (Table 1). Seven patients had anisocoria of less then 0.25 mm, whereas three had anisocoria of greater than 1.0 mm. The degree of anisocoria was exaggerated by repetitive light stimulation or by psychosensory stimuli. The psychosensory response was absent on the affected side in all but three patients, and in these three, it was markedly reduced in comparison to the normal side. At the termination of the series of light stimuli, the affected pupil had a delayed recovery toward its initial size, contributing to an exaggeration of the anisocoria.

Pharmacologic testing in 19 of the 21 patients with abnormal findings on pupillograms allowed separation into two groups: those with complete postganglionic sympathetic denervation and those with incomplete denervation (Table 2). Complete sympathetic denervation was found in five patients who had no mydriatic response to cocaine on the involved side but a good response to dilute epinephrine, indicating denervation with supersensitivity. Only one patient in this group was tested on separate occasions with cocaine and with hydroxyamphetamine, and this patient had no mydriatic response to either drug.

TABLE 1

EXTENT OF ANISOCORIA IN 21 PATIENTS WITH IMPAIRED INTRAOCULAR SYMPATHETIC INNERVATION

| Anisocoria | Dark | | Background Light | |
|---|---|---|---|---|
| | Mean (in mm) | SE | Mean (in mm) | SE |
| Initial | 0.57 | 0.08 | 0.61 | 0.08 |
| After three light stimuli | 0.95 | 0.11 | 0.91 | 0.10 |
| Increase with light stimulation | 0.37 | 0.06 | 0.31 | 0.05 |

In 14 patients, incomplete postganglionic sympathetic denervation was indicated by pupillographic abnormality and reduced mydriatic response to either cocaine or hydroxyamphetamine. Either drug produced an average mydriatic response that was less than half of the response of the normal pupil. There was no significant difference between the average response to cocaine and the average response to hydroxyamphetamine for the groups that received these drugs alone or for the five patients who received each drug on separate occasions.

Intraocular pressures, recorded for 16 of the patients, were lower by 2 to 6 mm Hg on the side with oculosympathetic paresis in

TABLE 2

MYDRIATIC RESPONSE OF PUPILS TO PHARMACOLOGIC TESTING

| Drug | Ocuolosympathetic Paresis | | | | Normal Pupil | |
|---|---|---|---|---|---|---|
| | Complete | | Incomplete | | | |
| | Mean (mm) | SE | Mean (mm) | SE | Mean (mm) | SE |
| Cocaine (4%) | −0.10 (n=5) | 0.03 | +0.50 (n=14) | 0.11 | +1.62 (n=19) | 0.20 |
| Epinephrine (0.1%) | +1.78 (n=5) | 0.41 | — | — | — | — |
| Hydroxyamphetamine (1%) | −0.32 (n=1) | — | +0.63 (n=6) | 0.09 | +1.45 (n=7) | 0.16 |

three patients, all of whom had incomplete sympathetic denervation. In the remaining 13 patients tested, intraocular pressures were equal in both eyes.

## Comment

Cluster headaches are considered a variant of migraine or vasodilating headaches in which the transient vasodilatory phenomena responsible for the syndrome are limited to the distribution of the carotid artery.[3] Experimental studies have demonstrated that, in some patients, dilatation of the branches of the external carotid reproduces pain in the typical region involved by the headaches and that, clinically, dilatation and tenderness of the temporal artery may occur, as well as flushing of the skin on the affected side. In other patients, however, the pain is reproduced by dilatation of the internal carotid artery and its branches.

In evaluating ocular signs associated with cluster headaches, Kunkle and Anderson[8] observed transient miosis during attacks in seven patients, while eight of their patients had permanent signs of oculosympathetic paresis with blepharoptosis and miosis. Two patients observed by these authors during an attack,[10] as well as one observed by Cogan,[11] each had a dilated pupil that later returned to normal size, thus suggesting a transient irritative sympathetic lesion. In attempting to explain the transient and permanent changes in pupillary size, these authors postulated a combination of sympathetic paresis, which probably occurs in the region of the carotid siphon where dilatation of the artery within the bony canal would injure the internal carotid plexus, and of parasympathetic discharge, which would contribute to the transient miosis, lacrimation, and rhinorrhea.[10] Nieman and Hurwitz,[5] however, stated that the miosis noted during attacks appeared to be solely the result of sympathetic dysfunction and that there was little evidence that parasympathetic discharge was responsible for this change.

All of our patients had permanent oculosympathetic paresis at the time of their evaluation; each of them had been aware of blepharoptosis on the involved side. Some patients remarked that this had been a transient phenomenon initially, occurring only with headaches for a varying time before becoming permanent; the majority were aware of the permanent narrowing of the palpebral fissure after their first episode of headaches. A few patients had permanent narrowing of the fissure only after many years of the attacks. The degree of narrowing of the palpebral fissure is consistent with the narrowing observed in Horner's syndrome due to a postganglionic sympathetic lesion or induced by blockade of the postganglionic oculosympathetic fibers.[9] The narrowing is due to involvement of the sympathetic innervation of both the upper and lower eyelids.

Dissociation of eyelid and pupillary involvement was found in three of our patients with typical narrowing of the palpebral fissure but normal pupillary and pharmacologic responses. This has been mentioned by other authors,[5,8] who have observed blepharoptosis or miosis alone, or blepharoptosis associated with miosis. The dissociation suggests that there may be a separation within the internal carotid plexus of the fibers innervating eyelids and pupil and that selective injury results in this dissociation.

Most of our patients were found by pupillography to have dysfunction of pupillary sympathetic innervation. On the basis of responses to topical pharmacologic testing, we have interpreted this as complete or incomplete postganglionic sympathetic denervation. Cocaine and hydroxyamphetamine are both indirect-acting sympathomimetic agents, and a mydriatic response to these drugs is predicated on the presence within the iris of intact sympathetic neurons that contain stores of norepinephrine. The mechanism of action of the two drugs, however, is different. Cocaine blocks the uptake mechanism of the presynaptic neuronal membrane, which is primarily responsible for terminating the action of norepinephrine (which has been released ei-

ther spontaneously or by nerve stimulation); cocaine does not by itself cause a release of norepinephrine from the neuron or its storage vesicles. Hydroxyamphetamine, however, acts by a competitive displacement of norepinephrine from presynaptic storage vesicles; its sympathomimetic activity depends only on intact sympathetic neurons and has no relationship to the rate of liberation of norepinephrine from the neurons. The usefulness of hydroxyamphetamine and similar indirect-acting agents such as tyramine as pharmacologic indicators for evaluating oculosympathetic innervation recently has been emphasized by Thompson and Menscher.[12] Although cocaine has commonly been utilized for such evaluation, the results may be difficult to interpret because a response depends not only on intact sympathetic neurons but also on the rate at which transmitter is released. With hydroxyamphetamine, any variability due to the rate of release of transmitter is eliminated. For this reason, we have utilized hydroxyamphetamine with increasing frequency in evaluating oculosympathetic paresis.

When complete sympathetic denervation occurs, there is no response to indirect-acting sympathetic drugs, and a supersensitivity to direct-acting sympathomimetic agents such as epinephrine and phenylephrine develops. Five of our patients had findings consistent with complete postganglionic sympathetic denervation and supersensitivity, for there was no reaction to cocaine or hydroxyamphetamine but a prompt mydriatic response to dilute epinephrine. Fourteen patients had a subnormal response to cocaine or hydroxyamphetamine, which we interpret as evidence of incomplete postganglionic sympathetic denervation. In support of this interpretation is the observation that two of the patients had segmental mydriasis only, limited to less than 30% of the circumference of the iris.

The observations regarding oculosympathetic paresis in these 24 patients and the variations in the extent of sympathetic dysfunction seem consistent with the supposition that injury to the internal carotid plexus occurs during the episodic dilatation of the artery that produces the headache. Anatomically, the most likely site for this injury is along the intraosseous portion of the internal carotid,[5,8] with variation in the extent of sympathetic involvement that may be related to the distribution of the fibers constituting the internal carotid plexus. Alternatively, one would have to postulate focal lesions occurring at different levels of the internal carotid plexus to explain the variation in sympathetic involvement. Data from our group of patients indicate that patients more likely will develop incomplete sympathetic denervation involving the eyelids and pupil, or the eyelids alone, rather than complete oculosympathetic denervation.

The incidence of permanent oculosympathetic paresis in patients with cluster headache evaluated at the Mayo Clinic is approximately 5%, which is comparable to the group reported by Kunkle and Anderson[8] (about 8%) but considerably less than that recorded by Nieman and Hurwitz[5] (22%), who commented on the selective bias which accounted for their high incidence. In the past seven years, more than 245 patients have been evaluated in the Pupillography Laboratory for Horner's syndrome or oculosympathetic paresis. Cluster headaches and associated oculosympathetic paresis account for approximately 10% of this group, and constitute one of the largest categories in which a specific etiologic diagnosis can be assigned to Horner's syndrome. For comparison, in patients evaluated in the Pupillography Laboratory, Horner's syndrome due to a malignancy represents less than 3% of the entire series (unpublished observation). This incidence is strongly biased by the selection and referral of patients for pupillography.

## Summary

Twenty-four patients with oculosympathetic paresis associated with cluster head-

aches were studied by infrared electronic pupillography and pharmacologic testing. Sympathetic dysfunction varied from paresis of the sympathetic innervation of the eyelids alone to complete postganglionic denervation of the eyelids and iris with denervation supersensitivity; most of the patients had incomplete postganglionic sympathetic denervation. These findings are consistent with the supposition that injury of the internal carotid plexus during the headaches results from dilatation of the intraosseous portion of the internal carotid artery.

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# GUARDED THERMAL SCLEROSTOMY

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An overfunctioning sclerocorneal fistula is the most frequent cause of complications following filtration surgery. These complications include hyposecretion with resultant risk of failure of filtration, choroidal detachment, macular edema, cataractogenesis, synechia formation, and corneal endothelial damage causing stromal edema. By the suture technique to be described, the surgeon is able to control aqueous flow through the surgically produced stoma during the early postoperative period, thus diminishing the problem of a flat anterior chamber.

The established surgical method of correcting the problem of an overfunctioning sclerocorneal fistula is usually quite effective and involves the injection of air into the anterior chamber, accompanied, when necessary, by posterior sclerotomy and drainage of subchoroidal fluid. However, it is desirable to have a method of avoiding the flat anterior chamber in order to obviate the attendant trauma to both the patient and the surgeon resulting from a second trip to the operating room so soon after a primary procedure.

More recently, the microsurgical techniques of trabeculectomy, trabeculotomy, and sinusotomy have been introduced. One of the major advantages of these techniques is to obtain a surgically produced pressure-lowering effect without causing a flat chamber. These techniques, however, are more difficult to perform than routine filtration procedures and require an intimate knowledge of the minute structure of the limbal area as well as familiarity with microsurgical techniques.

Various nonoperative techniques which usually involve tamponade of the bleb area have been suggested. Gehring[1] devised a bandage which exerted pressure over the bleb by its position on the upper eyelid. Chandler and Simmons[2] have tried several scleral contact shells and conjunctival suture techniques in an effort to flatten the bleb and thus prevent unimpeded drainage of aqueous from the chamber.

These methods, though frequently effective, have the disadvantages of being cumbersome, uncomfortable, or too inflexible to meet varying postoperative conditions. They are, however, useful in other types of filtration surgery while the procedure to be described here can effectively close only the slit-like opening of a thermal sclerostomy. We believe the guard suture avoids the above-mentioned disadvantages while remaining simple, effective, and relatively free of complications.

The evolution of this procedure began 15 years ago as an extension of a technique advocated by Dr. William Ferguson of San Francisco. In those narrow-angle eyes suspected of having associated trabecular damage, he suggested performing a peripheral iridectomy in the routine manner. On the third postoperative day, if the pressure remained elevated, he removed the suture closing the sclerocorneal incision in hopes of obtaining filtration. In 1960, Dr. Thomas Pettit expanded this idea and performed a procedure similar to the one to be described here on a small series of patients. It was also per-

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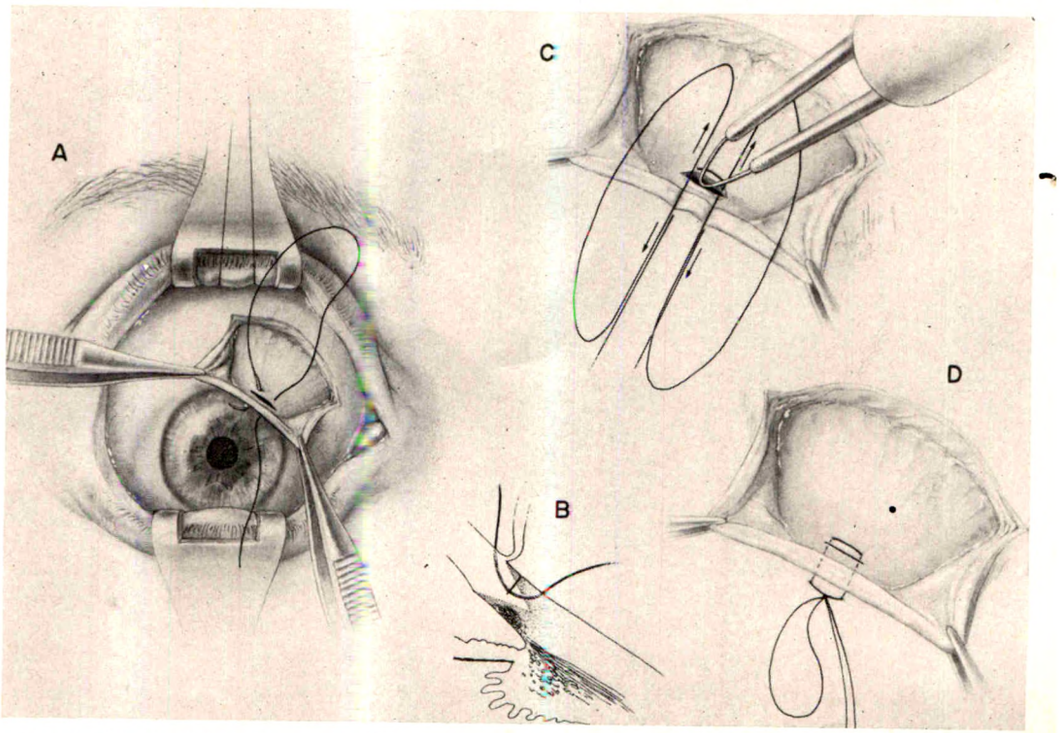



Fig. 1 (Shaffer, Hetherington, and Hoskins). (A) Path of suture across limbal incision. (B) Suture passes beneath conjunctival flap. (C) Loops withdrawn from incision and used for traction. (D) Mattress suture tied on corneal side with surgeon's knot secured by single bow knot.

formed by Becker and Shaffer[3] in the early 1960s, but it is only within the past few years that it has been used with any frequency.

## Technique

Thermal sclerostomy is a procedure familiar to most ophthalmic surgeons and will be described only briefly:

A large limbus-based conjunctival flap is fashioned in the upper nasal quadrant. The usual 3-4 mm incision is made through the outer two-thirds of the surgical limbus and cautery is applied to the wound edges. A 7-0 black silk suture double-armed with 3/8 circle reverse cutting needles (Ethicon G-6, Davis & Geck CE 20) is then passed into clear cornea at a point 2 mm anterior to the conjunctival flap. It is guided posteriorly at a depth of one-half the corneal thickness, passing beneath the limbal insertion of the conjunctiva to emerge in the incision at the junction of its middle and medial thirds. It is continued through the posterior lip of the wound to emerge from the sclera 1.5 mm behind the incision (Fig. 1-B). The return passage of the suture reverses the route, passing through the sclera, crossing the incision at the junction of its middle and lateral thirds to emerge from the cornea 2 mm anterior to the conjunctival insertion (Fig. 1-A). Thus, a firm mattress guard suture has been placed across the limbal incision with its free ends emerging from the cornea anterior to the conjunctival flap. At no time is the flap perforated. The transincision portions of the suture are then withdrawn from the wound and used for traction while the operation proceeds (Fig. 1-C).

The incision is deepened by sharp dissection interspersed with applications of cautery. After entering the anterior chamber, an iridectomy is performed. A surgeon's knot is then fashioned in the guard suture, and,

while the operator fills the anterior chamber with balanced salt solution, the assistant tightens the knot to approximate the wound edges and form the chamber. The surgeon's knot is secured with a single bowknot (Fig. 1-D). The conjunctival flap may be closed with continuous or interrupted 7-0 black silk sutures and the eye is patched. To facilitate manipulation of the suture during the postoperative period, the ends should be left 2 cm long. Subsequent adjustments of the suture can then be easily performed in the office under topical anesthesia.

At the first postoperative dressing, the eyes will have a formed chamber and 50% will have a bleb present. This is the ideal situation, and the suture should remain undisturbed until the fifth postoperative day, when both the bow and surgeon's knot are loosened. If the chamber remains formed for two days, the suture may be removed. If, however, the chamber should flatten, the suture should be re-tied to be loosened again in while the operator fills the anterior chamber two days.

In those eyes with a formed chamber but no evidence of bleb formation by the second postoperative day, both knots are loosened and a bleb usually forms spontaneously. If the bleb does not form with the suture loosened, gentle pressure on the cornea has rarely failed to form one. The suture should then be left in place, untied, until the fifth postoperative day so that it may be tightened again should the chamber collapse. If this occurs, the suture is secured for two more days. This process may be repeated as necessary. These sutures have been left in place for as long as 14 days without adverse affects.

## Discussion

It is generally accepted that flow of aqueous through the corneoscleral stoma is necessary to maintain patency of the fistula by collagenolysis. Teng and associates[4,5] found degeneration of collagen around filtration wounds where collagen fibers were in direct contact with aqueous. However, they also found portions of fistulas with an endothelial lining which prevented the lysis of collagen. They suggested that this lining arose from the iris endothelium which gained access to the fistula when the chamber was flat postoperatively.

Bellows and Chinn,[6] and later Bietti,[7] demonstrated in experimental animals that free drainage of aqueous from the anterior chamber, rather than resulting in an increased flow, actually caused decreased production of aqueous by the ciliary body after the first hour, resulting in a marked diminution of flow from the anterior chamber.

Thus a freely draining fistula can result in diminished aqueous flow, cause a flat chamber, and increase the risk of ultimate failure of filtration.

Although these studies seem to indicate a theoretical advantage could be gained by utilizing the guard suture in open-angle glaucoma, in practice the results have not varied significantly from those achieved by standard filtration procedures.

In the eye with narrow-angle configuration, however, there is a definite indication for the use of this technique. In such a globe, there is always risk of precipitating malignant glaucoma. Deepening the anterior chamber at the end of the procedure prevents anterior displacement of the lens–iris diaphragm and allows good cycloplegia and mydriasis. These factors encourage the normal anterior flow of aqueous and diminish the likelihood of malignant glaucoma. It also decreases the probability of lens incarceration in these eyes. In those narrow-angle eyes with combined-mechanism glaucoma in which it is impossible to preoperatively differentiate outflow obstruction that is due to iris apposition from obstruction that is due to trabecular damage, this technique may be used with a lighter application of cautery. If, postoperatively, no significant opening of the angle can be seen by gonioscopy, or marked elevation of intraocular pressure occurs, the suture can be loosened to obtain filtration.

Similarly, in aphakic glaucoma there are distinct advantages of this technique. By pushing the hyaloid back, incarceration of vitreous in the fresh wound is avoided. Immediate reformation of the chamber also prevents vitreocorneal adhesions and, by allowing mobility of the iris, averts iridovitreal adhesions. The latter can result in aphakic pupillary-block glaucoma resistant to treatment.

## Summary

A technique utilizing a mattress guard suture to obtain a formed anterior chamber immediately following thermal sclerostomy has several advantages, both theoretical and practical. The postoperative adjustment of the suture in the office can be carried out without difficulty. In order to prevent malignant glaucoma and postoperative problems with the vitreous body, this technique should be used in eyes with narrow-angle configurations and in aphakic glaucoma. The results, although based on a small series of cases, are encouraging, and this technique appears to have a useful place in the arsenal of anti-glaucoma surgery.

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# COMPARISON OF THE EFFECT OF PROPRANOLOL, LIGNOCAINE, AND OTHER DRUGS ON NORMAL AND RAISED INTRAOCULAR PRESSURE IN MAN

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Propranolol (Inderal), an adrenergic beta-receptor blocking agent, is reported to reduce intraocular pressure in patients with chronic simple glaucoma.[1,2] The mode of action of propranolol was not elucidated, but it was suggested that the effect resulted from the action of propranolol on an adrenergic mechanism responsible for either the rate of formation of aqueous humor or on the facility for outflow. On the other hand, it was also demonstrated that topical application of isoprenaline and adrenaline will reduce intraocular pressure in man.[3-6] Consequently, propranolol may affect intraocular pressure by actions not directly related to an effect on adrenergic receptors in the eye. In man, the systemic administration of propranolol reduces heart rate and cardiac output and increases total peripheral resistance[7]; as a consequence the rate of formation of aqueous humor may be reduced.

To eliminate the actions of propranolol on the systemic circulation, we have studied the effect of the drug on intraocular pressure by applying it directly to the eye. In addition to its adrenergic blocking properties, propranolol, is a potent local anesthetic.[8] As this property may also affect intraocular pressure, we have compared the effects of propranolol with those of lignocaine, MJ 1999 and INPEA. The latter two drugs block adrenergic beta receptors,[9] but which have no local anesthetic action.

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## METHODS

Observations were made in 62 hospitalized patients, 31 men and 31 women, all between the ages of 30 and 80 years. The patients were divided into three groups, according to diagnostic criteria:

*Group* 1. *Normal subjects*—These were 43 patients—(25 men and 18 women) admitted to the ophthalmic service for conditions not affecting intraocular pressure (e.g., conjunctivitis, dacryocystitis, central retinitis, strabismus, and cataract). These patients had not previously been given any drugs which might alter intraocular pressure.

*Group* 2. *Patients with chronic simple glaucoma*—The 12 patients belonging to this group (six men, six women) had monocular or binocular open-angle glaucoma as judged by field loss, tonometry, gonioscopy, visual acuity, and fundus observation. Prior to their present hospitalization, all had routinely used drugs commonly prescribed for the treatment of glaucoma, and after admission, treatment with these drugs was continued until the danger of an acute rise of intraocular pressure had passed. A period of at least five days elapsed after drug therapy ceased before the administration of propranolol began. Consequently, the intraocular pressures in these patients were not unduly high at the time observations were made (Table 1). In all patients in this group, the effects of the instillation of 0.9% saline was

TABLE 1

EFFECT ON INTRAOCULAR PRESSURE OF 0.9% SALINE IN PATIENTS WITH CHRONIC SIMPLE GLAUCOMA AND OF 2% PROPRANOLOL IN NORMOTENSION, CHRONIC SIMPLE GLAUCOMA, AND ACUTE GLAUCOMA

| Treatment Groups | Total No., Sex Patients | | Time (in minutes) Before and After Treatment | | | | | | | | | Statistical Significance (Controls vs Treated Patients) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | −60 | −30 | 0 | 30 | 60 | 90 | 120 | 150 | 240 | |
| Saline-treated controls: | | | | | | | | | | | | |
| Chronic simple glaucoma | 6-M | $\bar{x}$ mm Hg | 24.1 | 22.9 | 22.6 | 22.3 | 22.3 | 22.1 | 22.1 | 22.3 | 22.3 | $P>0.05$ |
| | | SE | ±1.8 | ±1.8 | ±1.6 | ±1.6 | ±1.6 | ±1.6 | ±1.6 | ±1.6 | ±1.6 | |
| | 6-F | $\bar{x}$ mm Hg | 23.9 | 23.0 | 22.8 | 22.3 | 22.4 | 22.4 | 22.3 | 22.3 | 22.3 | $P>0.05$ |
| | | SE | ±1.1 | ±1.1 | ±1.1 | ±1.2 | ±1.2 | ±1.2 | ±1.2 | ±1.2 | ±1.2 | |
| Propranolol-treated: | | | | | | | | | | | | |
| Normotensive | 9-M | $\bar{x}$ mm Hg | 15.5 | 15.3 | 15.3 | 13.1 | 11.2 | 9.8 | 9.4 | 10.4 | 11.8 | $P<0.01$ |
| | | SE | ±0.8 | ±0.9 | ±0.9 | ±0.8 | ±0.5 | ±0.3 | ±0.9 | ± 1 | ±0.7 | |
| | 9-F | $\bar{x}$ mm Hg | 15.8 | 15.8 | 15.8 | 15.8 | 14.8 | 13.9 | 14.0 | 14.4 | 14.7 | $P<0.01$ |
| | | SE | ±0.6 | ±0.6 | ±0.6 | ±0.6 | ±0.4 | ±0.8 | ±0.8 | ±0.7 | ±0.6 | |
| Chronic simple glaucoma | 6-M | $\bar{x}$ mm Hg | 22.0 | 21.6 | 21.2 | 18.3 | 16.6 | 16.5 | 15.7 | 16.0 | 17.5 | $0.01<P<0.05$ |
| | | SE | ±1.5 | ±1.5 | ±1.5 | ±1.4 | ±0.8 | ±0.7 | ±0.9 | ±0.9 | ±0.9 | |
| | 6-F | $\bar{x}$ mm Hg | 23.3 | 22.3 | 22.0 | 19.5 | 18.1 | 17. | 17.6 | 18.1 | 19.5 | $0.01<P<0.05$ |
| | | SE | ±1.1 | ±1.3 | ±1.4 | ±1.7 | ±1.7 | ±1.7 | ±1.6 | ±1.5 | ±1.3 | |
| Acute glaucoma | 7-F | $\bar{x}$ mm Hg | 65.5 | 65.5 | 65.5 | 65.0 | 65.0 | 65.0 | 63.2 | 63.2 | 63.9 | $P>0.05$ |
| | | SE | ±8.2 | ±8.2 | ±8.2 | ±8.4 | ±8.4 | ±8.4 | ±8.8 | ±8.8 | ±8.7 | |

studied on one day (as a control) and the effects of propranolol on the following day. The treatments were given in random order.

The patients in Groups 1 and 2 were randomly picked from the whole population of the ophthalmic service.

*Group 3. Patients with acute glaucoma*—Observations were made in seven women patients admitted to hospital with idiopathic or secondary acute glaucoma.

All patients remained in the supine position throughout periods of examination. Intraocular pressure was measured by a Schiøtz tonometer and expressed in mm Hg. With the exception of the experiments in which the effects of lignocaine and propranolol were compared in both eyes of the same patients, local anesthesia of the cornea was produced by the instillation of 3 drops of lignocaine 10 seconds before making the first control observations. Anesthesia was maintained throughout the period of observation by the administration of lignocaine every 30 minutes. In all patients except those seven who had a different drug applied to each eye at the same time, an electrocardiogram was made and heart rate determined by measurement of at least 10 R–R intervals (R–R = interval between two subsequent R waves of the electrocardiogram). Arterial pressure was measured by auscultation using a sphygmomanometer applied to the left arm. Mean arterial pressure (mm Hg) was taken as diastolic pressure plus one-third of pulse pressure. Local anesthetic activity was measured on the human cornea by using the Aesthesiometer (Cochet and Bonnet, Ltd.) and expressed in conventional units. The comparison between the activities of the four compounds was made by using the Friedman rank test. Intraocular pressure, heart rate, and arterial pressure were measured every 30 minutes, and when steady values were obtained, one of the following solutions was administered: (1) three drops of propranolol HCl (2% solution), (2) three drops of MJ 1999 HCl (2% solution), (3) six drops of INPEA HCl (2% solution), or (4) three drops of sodium chloride (0.9% solution). Each solution was administered to the conjunctival sac. In order to control the influence of sex, eye laterality, and experimental times on the changes in intraocular pressure, heart rate, and arterial pressure induced by any

treatment, an analysis of variance was carried out on the data exhibited at 0, 30 and 60 minutes before treatment and 30, 60, 90, 120 and 150 minutes after treatment.

## Results

*Intraocular pressure*—The averaged results from the three groups of patients are shown in Figure 1 and Tables 1 and 2.

*Control observations*—The instillation of saline into the conjunctival sac did not cause any change in intraocular pressure in patients with chronic simple glaucoma.

*Normal subjects*—In 18 patients (nine men, nine women) with normal intraocular pressure, propranolol eye drops produced a progressive reduction in intraocular pressure. This was maximal 120 minutes after administration of propranolol and was highly significant ($p < 0.01$) when men and women patients were taken as one group. No difference in the response to propranolol instillation was observed between the right and left eyes, while a marked and highly significant difference was recorded between the two sexes ($p < 0.01$): the decreases in intraocular pressure was 39% for men and 19% for women (Table 1).

*Patients with chronic simple glaucoma*—Propranolol produced a marked and significant reduction in intraocular pressure ($0.01 < p < 0.05$) in this group which was maximal 120 minutes after treatment. The response was similar in both sexes and in right and left eyes (Table 1, Fig. 1).

*Patients with acute glaucoma*—In patients with monolateral acute glaucoma, the administration of propranolol had no effect on the intraocular pressure of the diseased eye (Tables 1 and 2, Figs. 1 and 2) whilst it decreased the intraocular pressure in the contralateral, normotensive eye to 73.5% of control.

*Heart rate and arterial pressure*—The mean heart rates (beats per minute) during the control period were 8 in normal subjects, 78 in patients with chronic simple glaucoma, and 82 in those with acute glaucoma. After the administration of saline to patients with chronic simple glaucoma and of propranolol to the others, heart rate fell (Fig. 1). The decrease was maximal at 90 minutes and was highly significant ($p<0.01$) in all groups; this response was similar in men and women. The mean value for arterial pressure was 109 mm Hg and did not alter significantly in any of the groups of patients following the administration of either saline or propranolol.

*Effect of experimental drug in normal subjects*—Observations were made in 14 patients (seven men, seven women) in whom three drops of MJ 1999 were applied to both eyes after a one-hour control period. The averaged results in these patients are given in Table 3. In both sexes the introcular pressure fell during the control period, but no further change occurred.

*Effect of INPEA in normal subjects*—Observations were made in 14 patients (seven men, seven women) and the averaged results are given in Table 3. The administra-

TABLE 2

COMPARISON OF EFFECT OF PROPRANOLOL IN EYES WITH ACUTE GLAUCOMA AND NORMOTENSIVE FELLOW EYES IN SAME PATIENTS

| Patient Status | No. Eyes | | Time (in minutes) Before and After Treatment | | | | | | | | | Statistical Significance (Controls vs Treated Patients) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 60 | −30 | 0 | 30 | 60 | 90 | 120 | 150 | 240 | |
| Acute glaucoma | 7 | $\bar{x}$ mm Hg | 65.5 | 65.5 | 65.5 | 65.0 | 65.0 | 65.0 | 63.2 | 63.2 | 63.9 | $P>0.05$ |
| | | SE | ±8.2 | ±8.2 | ±8.2 | ±8.4 | ±8.4 | ±8.4 | ±8.8 | ±8.8 | ±8.7 | |
| Normotensive | 7 | $\bar{x}$ mm Hg | 16.3 | 15.9 | 15.9 | 13.4 | 11.9 | 11.7 | 12.2 | 13.3 | 14.5 | $P<0.01$ |
| | | SE | ±1.60 | ±1.61 | ±1.61 | ±1.68 | ±1.32 | ±1.18 | ±1.30 | ±1.54 | ±1.52 | |

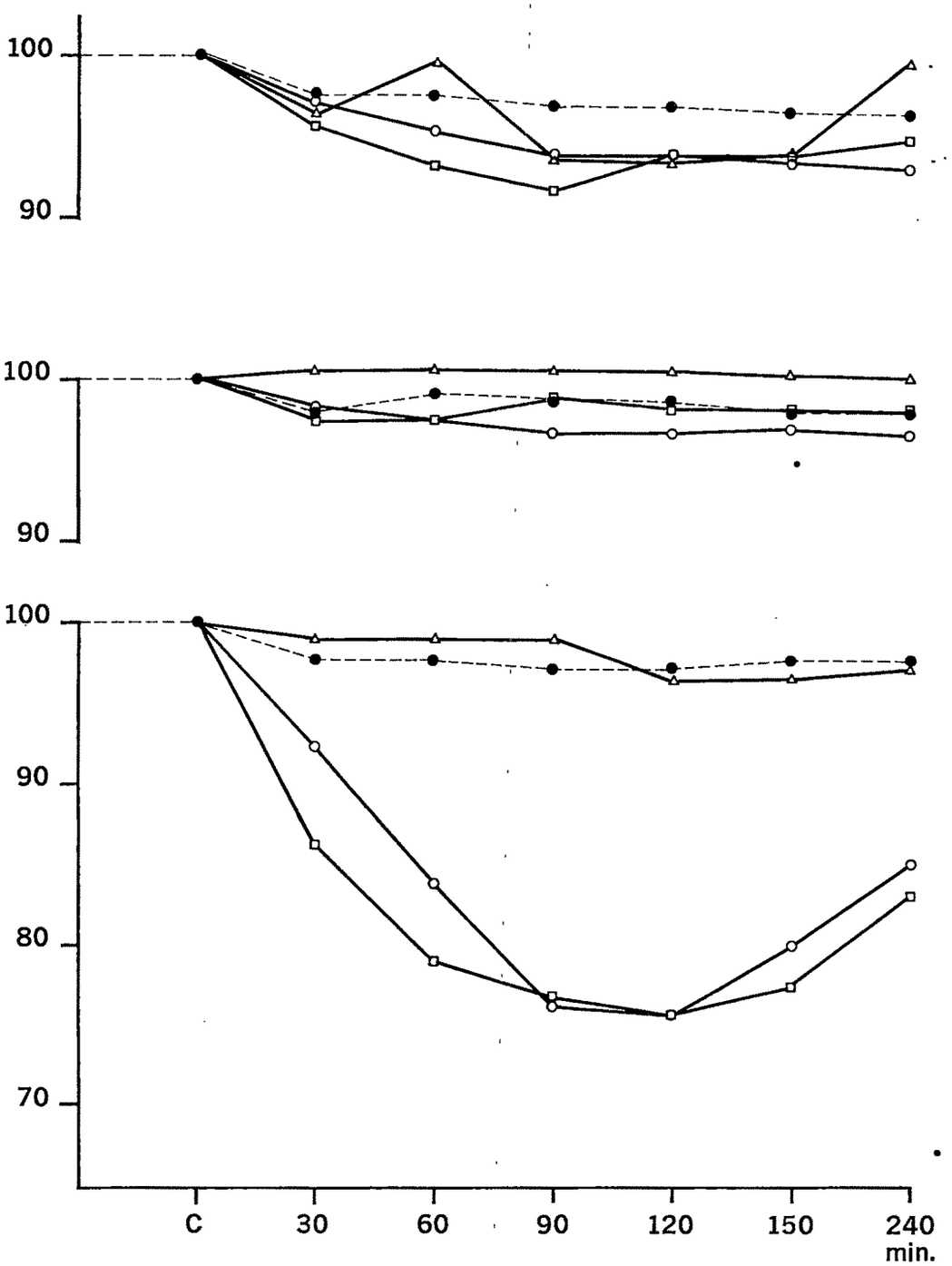



Fig. 1 (Musini and associates). Effects of saline (dashed lines) and propranolol 2% eye drops (solid lines) on heart rate (top), mean arterial pressure, (center), and intraocular pressure (bottom) in patients with normal intraocular tension (-○-), with chronic simple glaucoma (-□-) and with acute glaucoma (-△-). Variations are expressed as percent of control values.

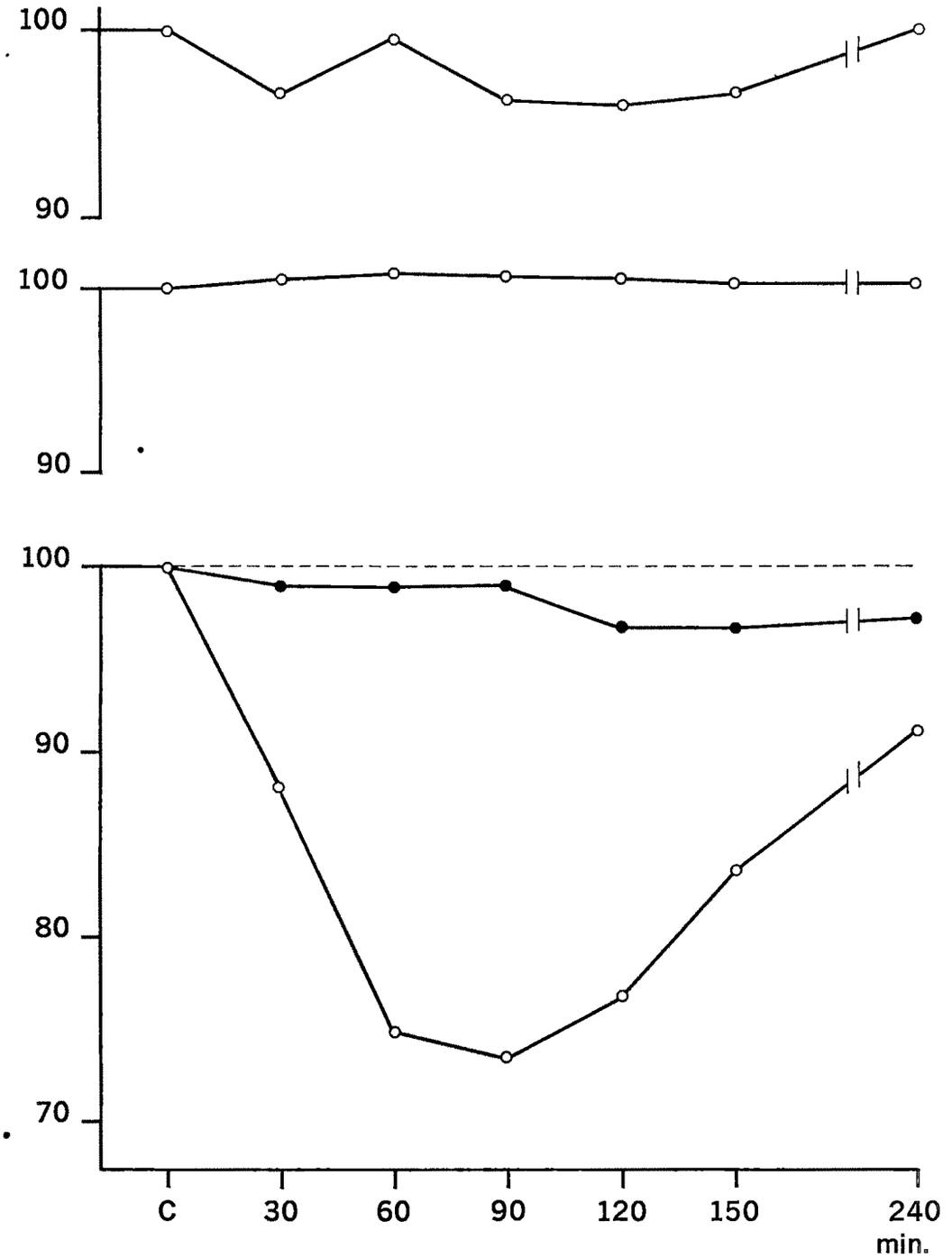



Fig. 2 (Musini and associates). Heart rate (top), arterial pressure (center), and intraocular pressure (bottom) responses to the instillation of propranolol 2% eye drops into the cojunctival sac of both the eyes with acute glaucoma (–•–) and the contralateral normotensive (–O–) eyes of the same patients. The curves are representative of the percent variations on the control values.

TABLE 3

EFFECT OF MJ 1999 AND INPEA ON INTRAOCULAR PRESSURE OF NORMOTENSIVE PATIENTS

| Treatments | Total No., Sex Patients | | Time (in minutes) After Treatment | | | | | | Controls | Statistical Significance (Controls vs Treated Patients) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 30 | 60 | 90 | 120 | 150 | 240 | | |
| MJ 1999* | 7-M | $\bar{x}$ mm Hg | 12.6 | 13.2 | 13.2 | 12.9 | 12.9 | 12.9 | 13.3 | P>0.05 |
| | | SE | ±0.8 | ±0.7 | ±0.8 | ±0.7 | ±0.7 | ±0.7 | ±0.9 | |
| | 7-F | $\bar{x}$ mm Hg | 15.3 | 15.4 | 15.4 | 15.4 | 15.4 | 15.4 | 15.4 | |
| | | SE | ±0.6 | ±0.6 | ±0.6 | ±0.6 | ±0.6 | ±0.6 | ±0.6 | P>0.05 |
| INPEA† | 7-M | $\bar{x}$ mm Hg | 12.9 | 12.2 | 12.6 | 12.6 | 12.6 | 12.3 | 12.8 | |
| | | SE | ±0.7 | ±0.6 | ±0.7 | ±0.7 | ±0.7 | ±0.7 | ±0.8 | P>0.05 |
| | 7-F | $\bar{x}$ mm Hg | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.0 | 12.8 | |
| | | SE | ±0.4 | ±0.4 | ±0.4 | ±0.4 | ±0.4 | ±0.4 | ±0.8 | P>0.05 |

* Three drops of a 2% solution.
† Six drops of a 2% solution.

tion of six drops of INPEA had no effect on intraocular pressure in either sex.

*Local anesthetic effect on the cornea*—The effects of the four drugs, propranolol, lignocaine, MJ 1999, and INPEA, were compared in both eyes of 15 patients. Lignocaine was applied to one eye of all patients (either left or right at random) and either propranolol, MJ 1999, or INPEA was applied to the other eye. The averaged results are given in Figure 3. In the concentrations used, MJ 1999 and INPEA had no anesthetic effect. Propranolol and lignocaine were equally active and had a similar duration of action ($p>0.05$).

*Comparison of intraocular pressure effects*—Observations were made in seven patients with normal intraocular pressures. Propranolol and lignocaine were applied randomly to either eye of all patients. The drugs were applied every 30 minutes for 240 minutes and intraocular pressure was measured 15 seconds after each administration. The averaged results are given in Table 4 and Figure 4 and show that both the drugs lowered intraocular pressure; the effect was maximal at 120 minutes and was followed by a rise in pressure. There was no significant difference between the effect of the two drugs (Table 5).

## DISCUSSION

The present observations show that the topical administration of propranolol to the eye reduces intraocular pressure in patients with normotensive eyes and in those with chronic simple glaucoma. This result cannot be ascribed to propranolol-induced changes in systemic hemodynamics, as arterial pressure was unaltered after topical application of the drug to the eyes and heart rate decreased to some extent both in control and in propranolol-treated patients. The effect is apparently not due to blockade of adrenergic beta receptors, as MJ 1999 and INPEA administration had no effect on intraocular pressure. In patients with normotensive eyes both lignocaine and propranolol reduced intraocular pressure to the same extent.

In all patients with normotensive eyes and in those with chronic simple glaucoma, intraocular pressure fell during the control period during which lignocaine had been applied to the eye to enable the measurement to be made. Thus lignocaine would appear to reduce intraocular pressure in these patients

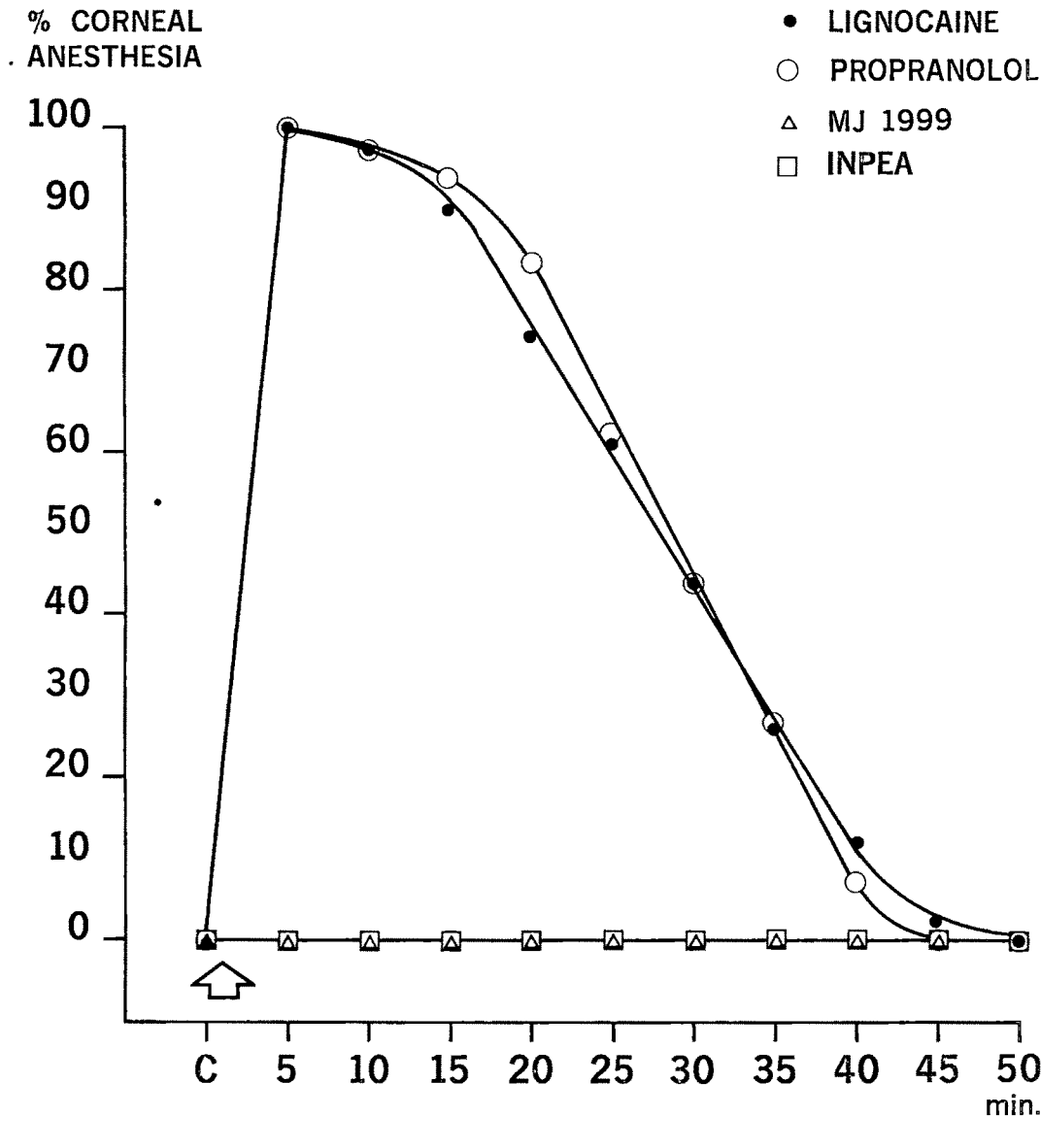



Fig. 3 (Musini and associates). Curves representing the intensity and duration of the local anesthetic activity of lignocaine (-O-), propranolol (-●-), MJ 199 (-□-), and INPEA (△). Each point is the mean value expressed as percent of the highest level of recorded from 15 healthy male subjects.

through its local anesthetic action. The present experiments have also shown that propranolol is as effective as lignocaine as a local anesthetic agent on the human cornea. These results all suggest that reduction in intraocular pressure produced by propranolol on topical application to the eye is due to its local anesthetic action. The present experiments do not explain the observations of Phillips and associates,[1] who reported a decrease in intraocular pressure after intravenous and oral administration of propranolol, as the local anesthetic action of propranolol on parenteral administration has not yet been determined in man.

There is also evidence from our results

TABLE 4

COMPARISON OF EFFECTS OF PROPRANOLOL AND LIGNOCAINE WHEN APPLIED CONTEMPORANEOUSLY TO FELLOW EYES

| Treatments | No. Eyes | | Time (in minutes) After Treatment | | | | | | Controls |
|---|---|---|---|---|---|---|---|---|---|
| | | | 30 | 60 | 90 | 120 | 180 | 240 | |
| Propranolol | 7 | $\bar{x}$ mm Hg | 15.6 | 15.1 | 14.5 | 14.0 | 14.2 | 15.1 | 16.9 |
| | | SE | ±0.46 | ±0.66 | ±0.80 | ±0.67 | ±0.77 | ±0.54 | ±0.57 |
| Lignocaine | 7 | $\bar{x}$ mm Hg | 14.8 | 14.1 | 13.8 | 13.2 | 14.5 | 15.1 | 15.8 |
| | | SE | ±0.34 | ±0.24 | ±0.22 | ±0.31 | ±0.58 | ±0.47 | ±0.36 |

that, when topically applied, both propranolol and lignocaine lower intraocular pressure when the iridocorneal angle is open, but not when the angle is closed, as in acute glaucoma. This conclusion is further supported by the evidence that propranolol and lignocaine decrease the intraocular pressure of the normotensive eye of patients whose contralateral eye is glaucomatous.

These findings suggest that the site of action of these drugs is in the chamber angle and that it involves a mechanism which can modify the resistance to outflow of the aqueous humor. The effect of these drugs may result from a reduction of the myogenic tone of the smooth muscle in the canal of Schlemm and in the other drainage channels, as the intra-arterial administration of propranolol and lignocaine reduce vascular smooth muscle tone.[11] Propranolol and ligno-

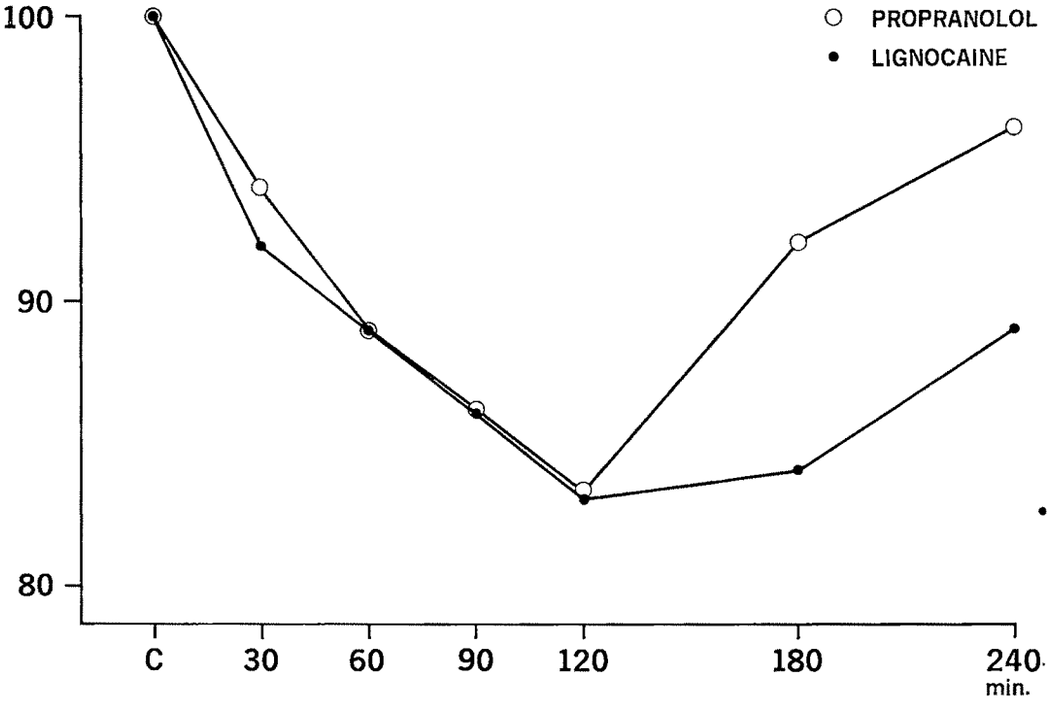



Fig. 4 (Musini and associates). Effects of propranolol 2% (-○-) and lignocaine 2% (-•-) on intraocular pressure of healthy male subjects. Variations are expressed as percent of control values.

TABLE 5

RESULTS OF THREE-WAY ANALYSIS OF VARIANCE OF DATA CONCERNING PERCENT INTRAOCULAR PRESSURE CHANGES INDUCED BY LIGNOCAINE AND PROPRANOLOL CONTEMPORANEOUSLY APPLIED AT RANDOM TO EITHER EYE OF THE SAME PATIENT

| Source of Variation | Degree of Freedom | Mean Squares | F* | Statistical Significance |
|---|---|---|---|---|
| Drugs | 1 | 2.2517 | 1.09 | P>0.05 |
| Patients | 6 | 2.9273 | 1.41 | P>0.05 |
| Drugs-patients interaction | 6 | 2.0689 | — | — |
| Times | 5 | 1.8881 | 5.30 | P<0.01 |
| Times-patients interaction | 30 | 0.3562 | — | — |
| Drugs-times interaction | 5 | 0.2908 | 1.37 | P>0.05 |
| Residual (drugs-times-patients interaction) | 30 | 0.2122 | — | — |

* F = Variances ratio (Fisher's test).

caine have also been observed to depress the myogenic activity of the isolated rabbit ileum.[11]

## SUMMARY

When the mechanism underlying the hypotensive action of propranolol on intraocular pressure was investigated in three groups of ophthalmic patients, propranolol, applied topically, decreased intraocular pressure in the normotensive eyes and in those with open-angle glaucoma, but not in eyes with acute glaucoma. Two beta-adrenoceptor blocking drugs which have no anesthetic activity, MJ 1999 and INPEA, did not alter intraocular pressure. When propranolol was applied to one eye and lignocaine to the other contemporaneously in normotensive patients, the two drugs were found to be equally potent in decreasing intraocular pressure. The present results suggest that the reduction in intraocular pressure consistently observed after topical application of propranolol to the eyes is due to the strong local anesthetic action of this drug.

## ACKNOWLEDGMENTS

The propranolol used in these experiments was supplied as Inderal (Imperial Chemical Industries, Ltd.) eye drops by Vister, Ltd., MJ 1999 (Sotalol) is a product of Mead Johnson, and the INPEA was supplied as eye drops by Selvi and Co., Ltd.

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# ACQUIRED AUTOSENSITIVITY TO DEGENERATING DESCEMET'S MEMBRANE IN A CASE WITH ANTERIOR UVEITIS IN THE OTHER EYE

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Acquired hypersensitivity to degenerative products of certain ocular tissues is an important factor in several serious eye diseases. Such diseases include phakoanaphylactic uveitis, sympathetic ophthalmitis, scleritis (necroscleritis nodosa, scleromalacia perforans, or massive scleritis), and giant cell arteritis (temporal arteritis). Hypersensitivity to degenerating Descemet's membrane may also develop, and this possibility, being apparently less well known, seems worthy of emphasis.

Hogan, Kimura and Thygeson[1] first reported the presence of foreign-body giant cells next to Descemet's membrane in cases of herpes simplex keratitis with stromal involvement. In 1964 and in 1967 reports by Zimmerman,[2] and Green and Zimmerman,[3] described similar observations in cases of longstanding ulcerative keratitis and suggested that the granulomatous reaction around Descemet's membrane might be indicative of an aquired autosensitivity to this structure. Green and Zimmerman[3] emphasized that Descemet's membrane is a remarkably permanent structure that resists the usual proteolytic enzymes released in corneal inflammations. They concluded that the granulomatous reaction around Descemet's membrane could be related either to a change in the physiochemical nature of Descemet's membrane or to the development of different proteolytic enzymes capable of its dissolution.

This paper presents a case in which there was a granulomatous inflammatory reaction to Descemet's membrane fragments which definitely showed evidence of dissolution. Clinical evidence of granulomatous uveitis in the other eye of this patient was of special interest.

## Case report

This 84-year-old white man was first seen in the Veterans Administration Hospital Eye Clinic in December, 1969, with a six-month history of corneal ulcer of the right eye. Initially, the eye was scratched by the branch of a fruit tree. Treatment with topical antibiotic eye drops proved unsuccessful. Examination revealed hand motion vision only in the right eye and normal vision in the left. The right eye was irritated and red, and a deep corneal ulcer extended over most of the lower half of the cornea. This was surrounded by corneal edema and neovascularization. Descemet's membrane was bulging and formed a broad descemetocele.

The patient was admitted. Cultures revealed coagulase-positive Staphylococcus aureus. Treatment with systemic and topical antibiotics plus calcium disodium EDTA was started. The cultures soon became negative, but the ulcer persisted. In January, 1970, a conjunctival flap procedure was performed over the lower half of the right cornea. This temporarily improved the condition and the patient was discharged. Over the next several months he remained comfortable, but the cornea continued to bulge and form a large corneal staphyloma with a paper-thin, opaque corneal layer (Fig. 1). There was definite evidence of slowly increasing chronic irritation and deep pain.

In May, 1970, a one-plus flare reaction was found in the anterior chamber of the previously normal left eye. This eye also exhibited multiple mutton-fat keratic precipitates (KPs). Topical corticosteroid and mydriatic therapy was started in the left eye and removal of the blind and irritated right eye was advised. The patient absolutely refused enucleation, but he finally permitted the blind eye to be eviscerated after being told that with this procedure the outer shell of the eye would be left in place. Evisceration of the right eye was accomplished without difficulties. Postoperatively recovery was uneventful. The left anterior uveitis quickly cleared and has not recurred.

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### Histopathologic study

The ocular contents of the right eye were composed of cornea, lens, and the collapsed uvea, retina, and vitreous. The thin cornea with its conjunctival covering was cut in cross sections. Histologically, it exhibited extreme thinning and neovascularization of the stroma. Fragmentation of Descemet's membrane was seen and this had caused many defects in this layer. Extensive granulomatous inflammatory reaction with giant cells, epithelioid cells, and a broad zone of mononuclear cells was seen in the region of the fragmented Descemet's membrane. Giant cells were found, especially next to and around the margins of the fragments of Descemet's membrane (Fig. 2). In many areas, the margins exhibited splitting of Descemet's glass membrane into two layers, and the most extensive granulomatous reaction was found in areas with this autolytic splitting (Fig. 3). More advanced destruction of Descemet's membrane also seemed to have caused a severe granulomatous inflammatory reaction (Figs. 4 and 5).

The iris was attached to the bulging cornea causing a total adherent leukoma. The lens exhibited cortical cataractous changes only and the lens capsule was intact. The retina exhibited diffuse atrophy and perivascular lymphocytic infiltration. It is important to emphasize that all of the uvea showed only a diffuse non-granulomatous inflammatory response, exhibiting dense lymphocytic infiltration (Fig. 6).

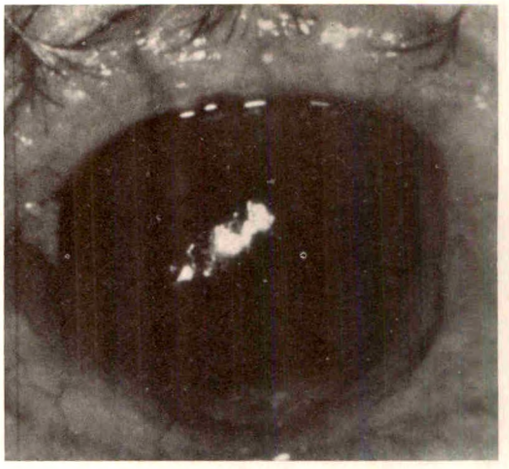


Fig. 1 (Wolter, Johnson, Meyer, and Watters). Right eye, showing staphyloma and adherent leukoma shortly before evisceration.

### Discussion

A rare combination of interesting findings is seen in the present case: fragmentation

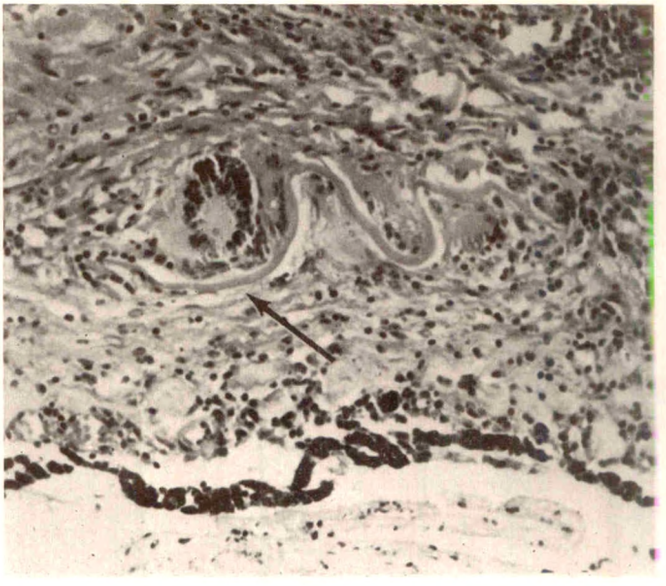


Fig. 2 (Wolter, Johnson, Meyer, and Watters). A fragment of Descemet's membrane (arrow) with a large giant cell near its deteriorating end. The iris is atrophic and firmly attached to the posterior corneal surface (paraffin section, hematoxylin and eosin, ×250).

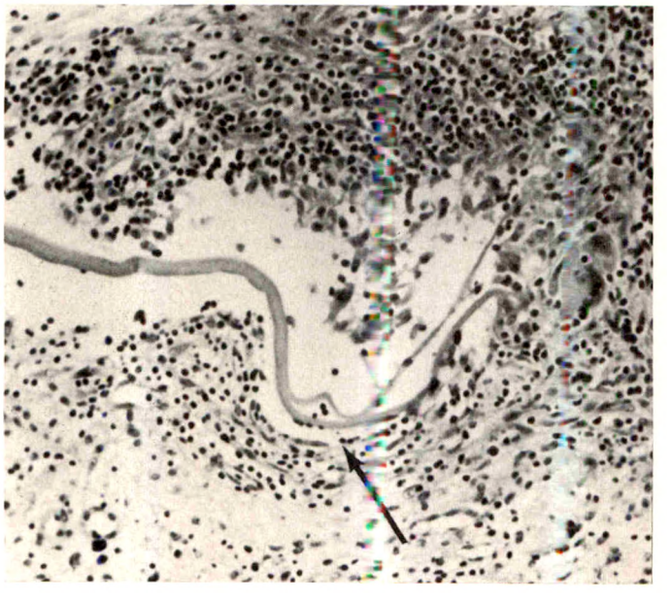


Fig. 3 (Wolter, Johnson, Meyer, and Watters). Autolytic lamellar splitting of Descemet's membrane (arrow) with granulomatous inflammation around it deep in the cornea (paraffin section, hematoxylin and eosin, ×250).

and autolytic splitting of Descemet's membrane, granulomatous inflammatory reaction centering on Descemet's membrane fragments, and clinical evidence of granulomatous anterior uveitis in the other eye.

Autolytic lamellar splitting of Descemet's membrane was observed long ago by anatomists in maceration studies.[4] Similar splitting has been described more recently as a late consequence of corneal trauma and degeneration.[5] Typical autolytic splitting of Descemet's membrane was observed in a case of a longstanding corneal ulcer in a 64-year-old patient (Fig. 7). The ulcer in this case was treated conservatively for several weeks and then covered with a conjunctival flap. Enucleation was finally necessary. Lamellar splitting of Descemet's membrane

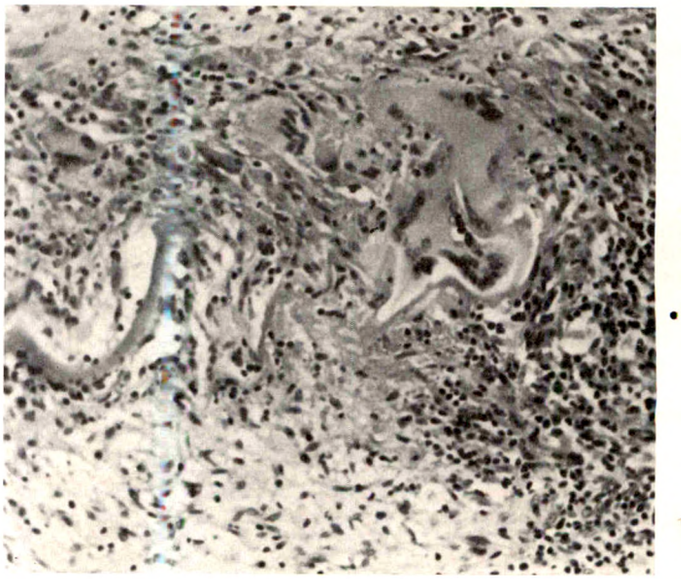


Fig. 4 (Wolter, Johnson, Meyer, and Watters). Large giant cells, epithelioid cells and lymphocytes around the degenerating edges of a fragment of Descemet's membrane deep in the cornea (paraffin section, hematoxylin and eosin, ×250).

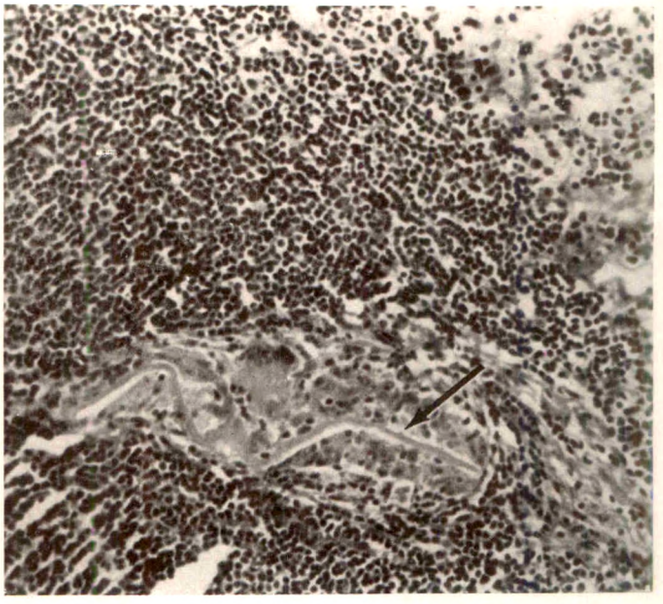


Fig. 5 (Wolter, Johnson, Meyer, and Watters). Low-power view of the localized granulomatous response around a fragment of Descemet's membrane (arrow) deep in the cornea (paraffin section, hematoxylin and eosin, ×100).

was found around the ruptured corneal ulcer.

The autolytic lamellar splitting in the present case indicates an advanced stage of deterioration of Descemet's membrane. This can be assumed to accompany the occurrence of protein breakdown products—much like those known to occur in the lens, for example, in situations that lead to a phakoanaphylactic uveitis.

The cases of Zimmerman and Green[2,3] showed little evidence of proteolytic changes in Descemet's membrane; whereas in contrast the present case shows advanced changes of this kind. This may indicate that the granulomatous reaction around Descem-

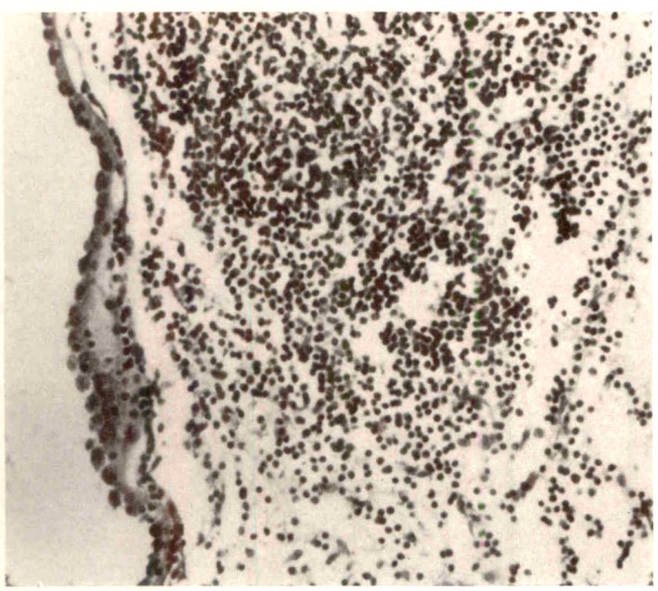


Fig. 6 (Wolter, Johnson, Meyer, and Watters). A portion of choroid and pigment epithelium exhibiting non-granulomatous chronic inflammation only (paraffin section, hematoxylin and eosin, ×250).

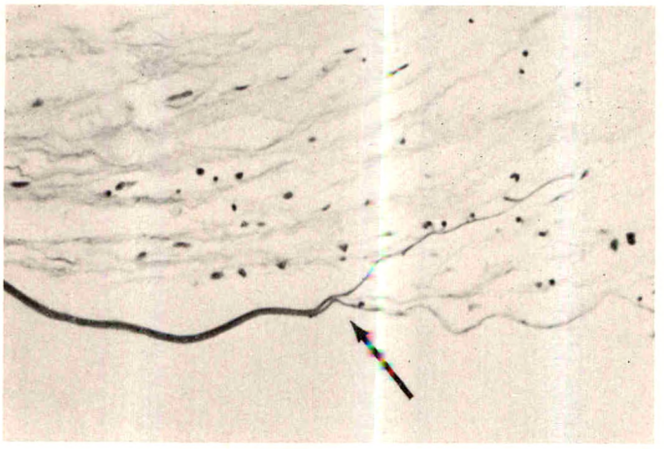


Fig. 7 (Wolter, Johnson, Meyer, and Watters). Typical autolytic lamellar splitting of Descemet's membrane (arrow) as seen in a second case with longstanding corneal ulcer (paraffin section, hematoxylin and eosin, ×250).

et's membrane fragments was not simply a foreign-body reaction, but that true hypersensitivity to breakdown products of this glass membrane had developed. Support for this theory is gained by a consideration of the factors surrounding the development of anterior uveitis with mutton-fat KP's in the other eye. In this connection it should be emphasized that the uvea of the primarily involved eye showed only non-granulomatous inflammation and that the granulomatous reaction was limited entirely to the deep cornea and seen next to Descemet's membrane fragments. The granulomatous reaction in the other eye might, thus, have been due to a generalized hypersensitivity to degenerated Descemet's membrane. This mechanism might resemble that of sympathetic ophthalmitis with its hypersensitivity to uveal pigment or that of phakoanaphylactic uveitis with hypersensitivity to degenerated lens. It is of great interest that ocular evisceration with complete removal of the cornea was apparently successful in eliminating the anterior uveitis in the other eye. It can be argued that specific generalized hypersensitivity can develop to degenerating Descemet's membrane and that this can cause a granulomatous reaction—possibly even involving both eyes.


## Summary

Fragmentation and autolytic lamellar splitting of Descemet's membrane in a blind eye with anterior staphyloma after longstanding corneal ulcer was found to have caused a localized granulomatous inflammatory response. Anterior granulomatous uveitis eventually developed in the other eye, but it cleared quickly upon evisceration of the staphylomatous eye and has not recurred. Both clinical and histologic evidence in this case suggest that a specific generalized hypersensitivity had developed to degenerating Descemet's membrane, thus causing the granulomatous inflammation in both eyes, an effect similar to that seen, for example, in sympathetic or phakoanaphylactic uveitis.


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# THE PATHOGENESIS OF CONGENITAL HEREDITARY ENDOTHELIAL DYSTROPHY OF THE CORNEA

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In a recent investigation of congenital hereditary corneal dystrophy occurring in a neonate,[1] histopathologic study disclosed a complete absence of endothelial cells except at the corneal periphery and a uniform thinning of Descemet's membrane. The present study describes the ultrastructural changes evident in the ocular tissues of this same infant.

## MATERIALS AND METHODS

The child died of respiratory insufficiency at the age of 36 hours. His eyes were enucleated about 13 hours postmortem, were fixed in formalin, and were embedded in paraffin. This material was subsequently prepared for electron microscopy by dissolution of the affin with chloroform, rehydration in veronal acetate buffer, dissection into suitably sized specimens, fixation in veronal-acetate buffered 2% osmium tetroxide, and embedding in Araldite. (This method, while unfortunately sacrificing much ultrastructural detail of the cellular components, does sufficiently preserve extracellular material for accurate electron microscopic study.[2]) Thin sections were cut on a Porter-Blum MT-2 microtome, doubly stained with uranyl acetate and lead citrate, and examined with a JEM 100-B electron microscope at 60 kv.

## RESULTS

*Corneal epithelium and Bowman's membrane*—In the anterior corneal layers, only the effects of chronic corneal edema are apparent (Fig. 1). These nonspecific changes include: (1) thinning of the corneal epithelium to three or four cell layers and probable hydropic change of the basal cells, (2) distension of the intercellular spaces by edema fluid, (3) occasional subepithelial microbullae in association with discontinuities of the epithelial basement membrane, and (4) surface irregularities of Bowman's membrane. Bowman's membrane is otherwise unaffected and appears as a layer ($\sim$ 15 $\mu$ thick) of randomly oriented collagen fibrils which display the usual cross-sectional diameter ($\sim$ 26 nm) and longitudinal periodicity (55-60 nm) of corneal collagen.

*Corneal stroma*—Stromal edema accounts for the marked swelling of the cornea to about three times normal thickness. Ultrastructurally, the deep stroma is most severely disorganized, as edema fluid has formed pools which grossly distort the lamellae. In the anterior stroma, although the lamellar pattern is generally maintained, the collagen fibrils are variably separated and displaced from their usual lattice-like orientation (Fig. 2). The individual collagen fibrils, however, seem entirely normal as they consistently measure 26-30 nm in diameter with $\sim$ 60 nm longitudinal periodicity. Swollen collagen fibrils of $>$ 30 nm diameter are nowhere evident. The stromal keratocytes are also unremarkable in appearance.

*Corneal endothelium and Descemet's membrane*—At the corneal periphery the cuboidal endothelial cells appear essentially normal, having formed a single continuous layer in close apposition to the posterior surface of Descemet's membrane (Fig. 4). In the mid-periphery of the cornea, however, the endothelial cells become attenuated and then abruptly disappear (Fig. 5). Beneath the central cornea, neither isolated endo-

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thelial cells nor cellular remnants are present (Fig. 6). Descemet's membrane, though appearing by light microscopy as a uniformly thinned layer (~3 μ thick—normal thickness in newborn humans = 4-6μ), actually displays significant ultrastructural variability which is seemingly dependent upon the condition of the endothelium. In particular, Descemet's membrane at the corneal periphery consists entirely of multiple layers of fine filamentous basement membrane-like material (each layer ~40-60 nm thick) interspersed with small diameter (~15 nm) collagen fibrils (Fig. 4). More centrally, at the point of endothelial termination, a thin layer of randomly oriented collagenous fibrils initially appears, covering the posterior surface of the multilayered Descemet's membrane (Fig. 5). Progressing toward the central cornea, this collagenous zone assumes greater prominence as it maximally constitutes about 80% of the overall thickness of Descemet's membrane, whereas the multilayered zone diminishes to a thin strip immediately subjacent to the stroma (Fig. 6). Despite the variable contributions of these two components, the overall thickness of Descemet's membrane remains remarkably constant.

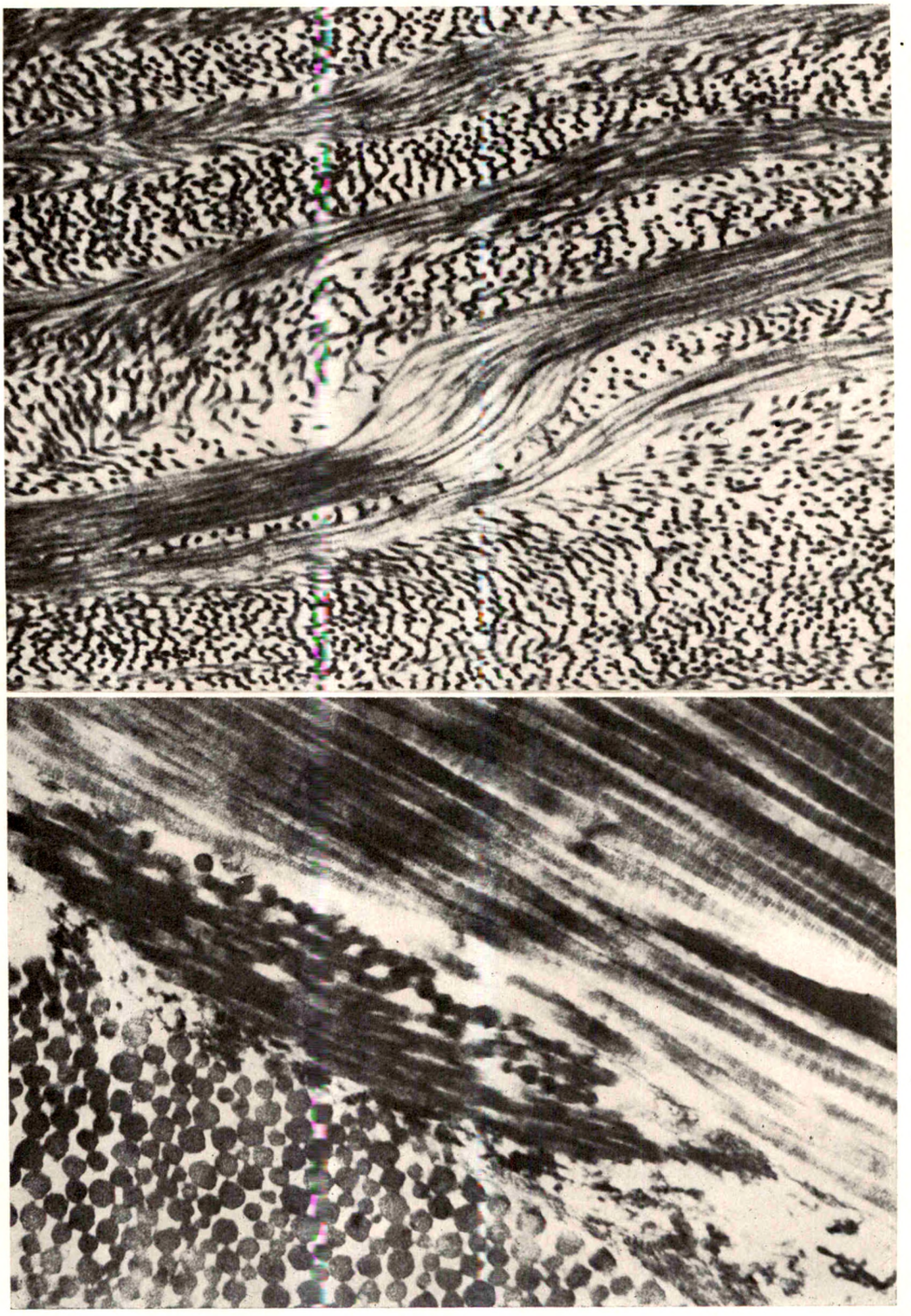
*Other ocular tissues*—In the sclera, the large collagen fibrils of ~75-120 nm diameter and ~60 nm longitudinal periodicity are entirely within normal limits (Fig. 3). The iris, ciliary body, and choroid also exhibit no significant ultrastructural abnormalities. Retinal tissue could not be evaluated by electron microscopy.

## Discussion

The pathogenesis of congenital disease is often best studied in the newborn, since in the neonatal period primary pathologic alterations are least obscured by secondary chronic sequelae. Among the above-mentioned ultrastructural observations of congenital hereditary corneal dystrophy in a neonate, the evidences of endothelial degeneration and the effects of stromal edema are most prominent. Accordingly, discussion will be limited to consideration of these key alterations as they relate to the pathogenesis of this corneal dystrophy.

*Endothelial degeneration*—In 1960, Maumenee[3] studied the histopathology of congenital hereditary corneal dystrophy in four patients (ages six to 22 years) and suggested the possibility that an endothelial defect might constitute the primary etiologic factor. The initial electron microscopy of this dystrophy[4] supported this hypothesis with the findings of a thin Descemet's membrane and an absent endothelium in the keratoplasty. More recently, Pearce and associates[5] were able to demonstrate by light and electron microscopy either an absence or a marked reduction of the endothelial cells in keratoplasty specimens from six patients (ages 37 to 71 years). In each of these reports, the possibilities of surgical damage, or aging changes of the endothelium, or both, could not be altogether excluded. Finally, however, the finding of a complete absence of the central corneal endothelium in the enucleated eye of a newborn[1] provided good histopathologic evidence that this dystrophy represents

Fig. 1 (Kenyon and Antine). The anterior layers of the cornea exhibit the changes of chronic corneal edema. The epithelium is thinned to three or four cell layers. Bridging dilated intercellular space, cytoplasmic processes of adjacent epithelial cells are joined by desmosomal attachments (circled). (The large cleft beneath the nucleus (N) of the basal cell is artifactitious.) Discontinuities (arrows) of the epithelial basement membrane (BM) are associated with surface irregularities of Bowman's membrane (Bow M). The randomly oriented collagen fibrils of Bowman's membrane are distinct from the organized collagenous lamellae of the stroma (S) (×7700).



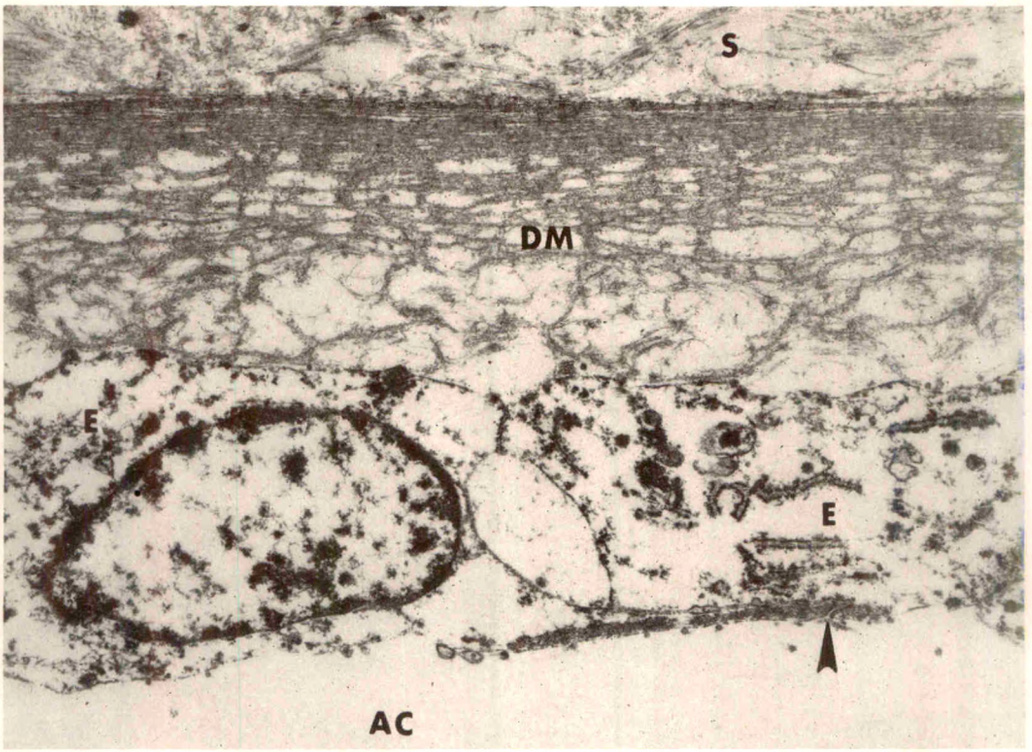


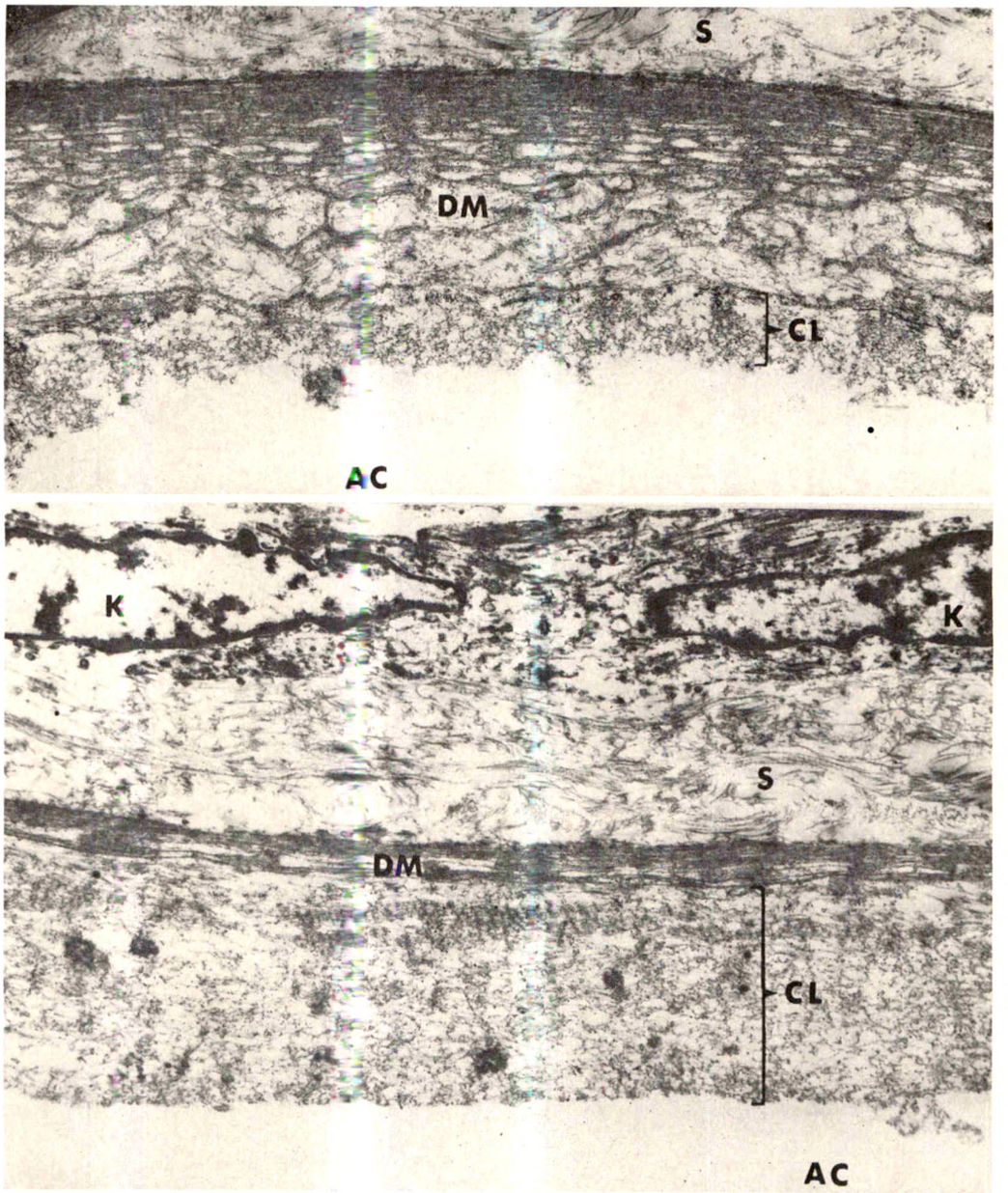

Fig. 4 (Kenyon and Antine). At the corneal periphery, the cuboidal endothelial cells (E) are joined by junctional complexes (arrow) to form a continuous layer in close apposition to Descemet's membrane (DM), which displays a multi-layered ultrastructure of basement membrane-like material throughout its entire thickness (S = stroma, AC = anterior chamber) (×12,000).

the clinical manifestation of an intrauterine degeneration of the corneal endothelium. The findings of the present electron microscopic study of ocular tissues from this same infant are in complete accord with this conclusion.

Comparison of the normal developmental appearance of Descemet's membrane with the abnormal ultrastructure of that membrane in this dystrophy provides additional insight into the progressive course of the endothelial degeneration. It is generally held that Descemet's membrane respresents the hyperplastic basement membrane of the endothelial cells. In the human embryo, Wulle and Lerche[6] have found that between the eighth and 14th weeks of gestation, Descemet's membrane initially appears as short, discontinuous segments of basement membrane-like

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Figs. 2 and 3 (Kenyon and Antine). In Figure 2 (top), edema in the anterior corneal stroma has produced some distortion of the lamellae and irregular separations among the collagen fibrils. The individual collagen fibrils are of normal diameter (26-30 nm) and longitudinal periodicity (~ 60 nm) (×40,000). In Figure 3 (bottom), the large collagen fibrils of the sclera show much greater variability of cross-sectional diameter (~75-100 nm) than in the cornea (see also Fig. 2 at same magnification). The longitudinal periodicity of about 60 nm is clearly visible (×40,000).




Figs. 5 and 6 (Kenyon and Antine). In Figure 5 (top), in the mid-periphery of the cornea, central to the termination of the endothelial cell layer, the posterior surface of Descemet's membrane (DM) is covered by a layer of collagenous fibrils (CL) (S = stroma, AC = anterior chamber) (×12,000). In Figure 6 (bottom), in the central cornea, no endothelial cells are evident. The multilayered zone of Descemet's membrane (DM) is markedly thinned, whereas the collagenous layer (CL) has become considerably thickened (see also Figs. 4 and 5 at same magnification) (×12,000).

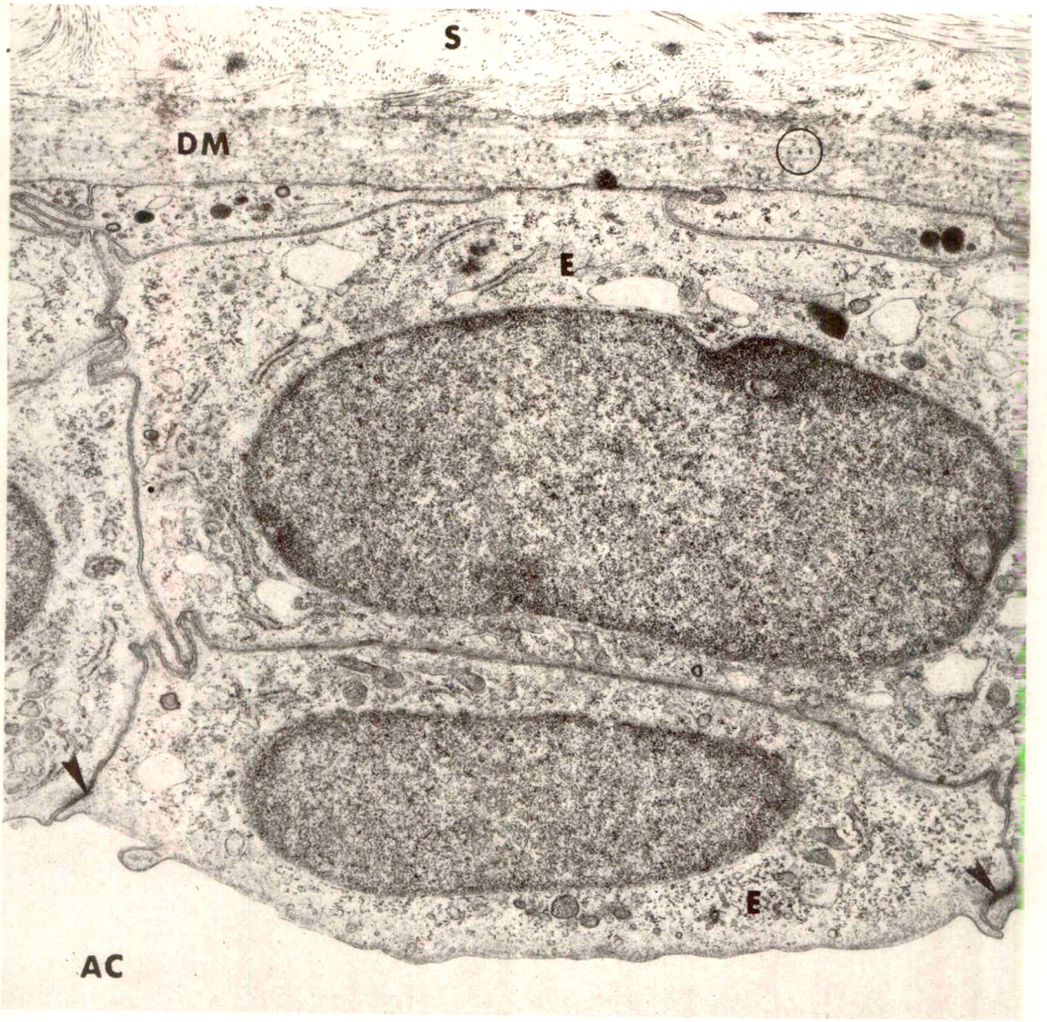



Fig. 7 (Kenyon and Antine). In the normal human fetus of 24 weeks' gestational age, the endothelial cells (E) assume a pseudo-stratified configuration, and well developed junctional complexes (arrows) have formed to seal the intercellular space from the anterior chamber (AC). Descemet's membrane (DM) is composed of several layers of basement membrane-like material, interspersed with fine collagen fibrils. Banding of 90-120 nm periodicity (circled) is evident (S = stroma) (×12,000).

material which coalesce to form a continuous lamina (measuring ~40-60 nm in thickness) lying immediately subjacent to the basal cell membrane of the endothelial cells. Subsequent development is depicted in Figure 7, which shows that in a human fetus of 24 weeks' gestation Descemet's membrane has progressed to about 1 μ in thickness and is composed of several layers of basement membrane (~50-70 nm thick) with fine collagen fibrils interspersed between the layers. The hexagonal organization pattern, which eventually confers a banded appearance upon the anterior portion of Descemet's membrane, is also evident here as electron-dense nodes which display 90-120 nm internodal periodicity. The later growth of Descemet's membrane presumably involves the deposition of additional basement membrane material, thereby increasing the thickness of this layer to 4-6 μ in the normal newborn infant and as much as 20 μ in the normal adult.

Prior to this report, keratoplasty specimens from three patients with congenital hereditary corneal dystrophy had been studied by electron microscopy. In all three specimens, an anterior banded zone of Descemet's membrane, measuring about 3-4 μ in thickness, was covered posteriorly by a non-banded collagenous layer of variable thickness, measuring $< 1$ μ in a 10-year-old boy,[4] about 14 μ in a 37-year-old woman, and about 30 μ in a 63-year-old woman.[5] If interpreted within the framework of normal corneal development, these alterations of Descemet's membrane in the preceding cases and in the present case seem consistent with the following conclusions:

1. The presence of a continuous Descemet's membrane over the entire posterior surface of the dystrophic cornea indicates that the endothelium is functionally intact through at least the third month of intrauterine development.

2. As demonstrated by the present case, the endothelial degeneration commences centrally and progresses peripherally, perhaps beginning after the fifth gestational month (as can be inferred by the comparable thicknesses of the multilayered Descemet's membrane in the central corneas of both the infant reported here and the normal 24-week fetus). In the other reported cases, the remarkably similar thicknesses of the banded zone of Descemet's membrane further localizes the onset of endothelial dysfunction to a relatively constant period in developmental time.

3. In areas where the endothelium is absent, a retrocorneal membrane of fine collagenous fibrils is formed which blankets the exposed multilayered or banded zone of normal Descemet's membrane and which apparently thickens with advancing age (to produce the misleading clinical and histologic impression of a thickened Descemet's membrane).

*Stromal edema*—In five patients with congenital hereditary corneal dystrophy, Kenyon and Maumenee[2,4] found that, in addition to the anticipated ultrastructural effects of chronic stromal edema, there was also a consistent swelling of the stromal collagen fibrils to almost twice normal diameter (measuring 41-49 nm as compared to a normal diameter of 24–26 nm). Sears has told us that he observed similar changes in the cornea of another patient with this dystrophy. Since stromal edema usually effects a swelling of the interfibrillar ground substance to produce nonuniform increases in spacing among collagen fibrils of normal dimensions, the stromal edema in congenital hereditary corneal dystrophy seemed, therefore, to constitute a distinct pathologic alteration.

Subsequently, however, Pearce and associates[5] were able to locate only a few corneal collagen fibrils of increased diameter in the corneas of two patients with congenital endothelial dystrophy which they studied by electron microscopy. In the present case as well, we have observed only collagen fibrils of the usual 26-30 nm diameter and these are accompanied by the usual changes of chronic stromal edema.

Unfortunately, the uncertainty over the pathologic significance of swollen stromal collagen is additionally confused by conflicting electron microscopic findings in several other diseases affecting the cornea. In particular, whereas various investigators have reported the occurrence of large-diameter collagen fibrils in the chronically edematous corneas of patients with metaherpetic keratitis and Fuchs' dystrophy (Offret and associates[7]), congenital glaucoma (Pouliquen and Saraux[8]) and Hurler's mucopolysaccharidosis (Pouliquen and associates[9]), others have not confirmed these observations. In our own study of stromal swelling,[2] we were unable to find enlarged collagen fibrils in corneas affected by congenital and secondary glaucomas, Fuchs' dystrophy, or systemic mucopolysaccharidosis (Hunter and Maroteaux-Lamy variants). The definitive resolution of these conflicting observations must await further careful study.

Finally, however, it is of speculative interest that the corneal endothelium itself might be a determinant of the size of the stromal collagen fibrils. Zinn,[10] who recently studied the effects of early lens removal in the chick embryo, found that following lentectomy a retrocorneal membrane formed which consisted of collagen fibrils with a diameter of about 50-60 nm. While that investigator attributed these changes as a specific response to lens removal, the failure of endothelial development in these embryonic corneas also suggests that the endothelium might influence stromal fibrillogenesis, an influence which could hold obvious implications for the endothelial dysfunction of congenital hereditary corneal dystrophy.

In conclusion, it is apparent that the weight of recent evidence now clearly favors the likelihood that congenital hereditary corneal dystrophy is a true primary dystrophy of the corneal endothelium which secondarily produces stromal and epithelial edema with concomitant corneal clouding. Therefore, in the interest of improving the etiologic classification of diseases, it would seem advisable to redesignate this disease entity as congenital hereditary endothelial dystrophy of the cornea.

## Summary

In an electron microscopic study of the ocular ultrastructure of a newborn infant with congenital hereditary endothelial dystrophy of the cornea, the pathologic alterations were found to include chronic epithelial and stromal edema, abnormalities of Descemet's membrane, and absence of the central endothelium. On the basis of these findings, the pathogenesis of this dystrophy is interpreted as follows: (1) There is a primary degeneration of the corneal endothelium which initially affects the central endothelium after the fifth month of gestation and subsequently progresses peripherally. (2) A secondary development is the diffuse stromal and epithelial edema which produces the clinically apparent clouding of the affected cornea.

## Acknowledgments

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# MALIGNANT MELANOMA OF THE CORNEA IN AN AFRICAN PATIENT

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Malignant melanoma of the cornea is a rare disease. Reports by Clune,[1] Stallard,[2] Lamers,[3] and Notter[4] among others, describe isolated cases. The case presented here involved the cornea first and later, the conjunctiva in a young African patient. Certain features are unusual, and it is thought that the melanoma could have arisen independently from cornea and limbal conjunctiva. While it is recognized that malignant melanomata of the uveal tract occur rarely in the pigmented races compared to Caucasians, malignant melanomata of the conjunctiva and the limbus do not show this difference. Malignant melanoma of the cornea has not been reported previously as occurring in the African, despite the increased pigmentation occurring naturally in the conjunctiva, limbus, and cornea.

Malignant melanoma occurred in the conjunctiva of the orbit in this patient 17 months after enucleation and the patient delayed in seeking further treatment for six additional months. By this time, enlarged pre-auricular and submandibular glands were present. The orbital contents were eviscerated and 18 months later, although he still has palpable and enlarged submandibular glands, there is no recurrence in the orbit and the patient remains alive and well. The other eye shows interesting changes with extensive pigmentation involving the basal cells of the corneal epithelium.

## CASE REPORT

A 23-year-old African, a Zulu man, reported to the outpatient department on August 1, 1967, because of a black mass on the right cornea which he said had been present for approximately three months. The mass protruded forward for about 5 mm. The conjunctiva appeared normal. It was noted that the cornea of the left eye was pigmented. The right eye was enucleated and the histologic report was that of a malignant melanoma of the cornea.

On June 10, 1969, the patient returned, presenting with a large black mass occupying the right orbit (Fig. 1) that he said had been present for six months. There were enlarged pre-auricular and submandibular glands. The left cornea now showed an irregular, pigmented surface (Fig. 2), with areas of thinning of superficial opacification. The left conjunctiva was normal. On June 16, 1969, the contents of the right orbit were exenterated. A biopsy was taken from a lymph node from the pre-auricular group of glands which, in conjunction with the submandibular group, looked black and tarry. Histopathology revealed the presence of metastatic malignant melanoma.

The state of the left cornea was now causing concern, as vision was deteriorating to the level of counting fingers. Biomicroscopy, showed irregularity of the superficial cornea with pigmentation. The cornea was thin with maximum pigmentation cen-



Fig. 1 (Welsh and Jhavery). Malignant melanoma of the right conjunctiva.

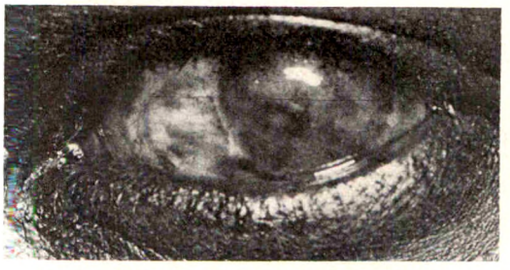


Fig. 2 (Welsh and Jhavery). Left cornea. Biomicroscopically, pigmentation was the main feature with no vascularization.

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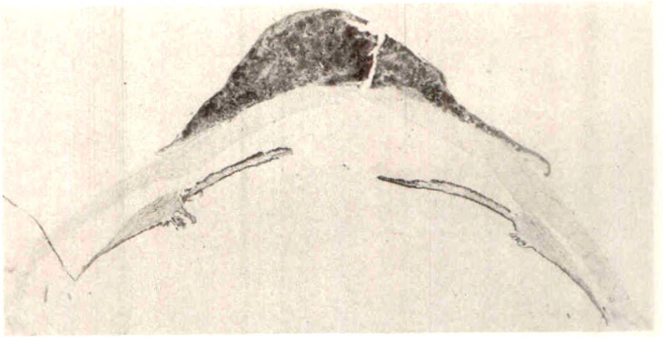


Fig. 3 (Welsh and Jhavery). Malignant melanoma of cornea (hematoxylin-eosin, ×6).

trally. The conjunctiva showed scattered areas of pigmentation in the exposed palpebral portion, but this was not considered to be abnormal. On February 3, 1970, a 7 mm penetrating corneal graft was performed.

Laboratory tests showed hemoglobin 13.4 g/100 ml, packed cell volume 42%, mean corpuscular hemoglobin concentration 32 g/100 ml, white blood cell count 7000, erythrocyte sedimentation rate 5 mm/hour. X-ray films of skull and chest were normal.

Systemic cytostatic drugs and radiotherapy were thought to be ineffective and to date (January 12, 1971), the patient is alive and well.

### Pathologic findings

*Right cornea*—The bulk of the tumor was found to be lying anterior to the corneal stroma. In parts it had penetrated through Bowman's membrane to involve corneal stroma (Fig. 3). Tumor cells containing melanin occurred in a predominately alveolar pattern. Superficial vascularization was present (Fig. 4). The tumor appeared to have arisen from the corneal epithelium.

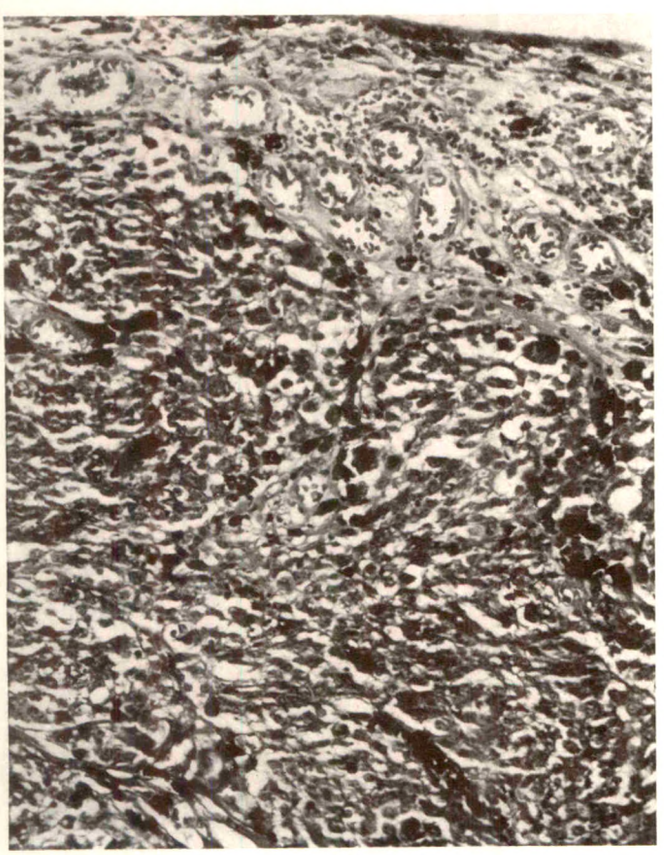


Fig. 4 (Welsh and Jhavery). Malignant melanoma of cornea. Pigmented cells arranged in alveolar pattern. Superficial vascularization of epithelial surface (hematoxylin-eosin, ×300).

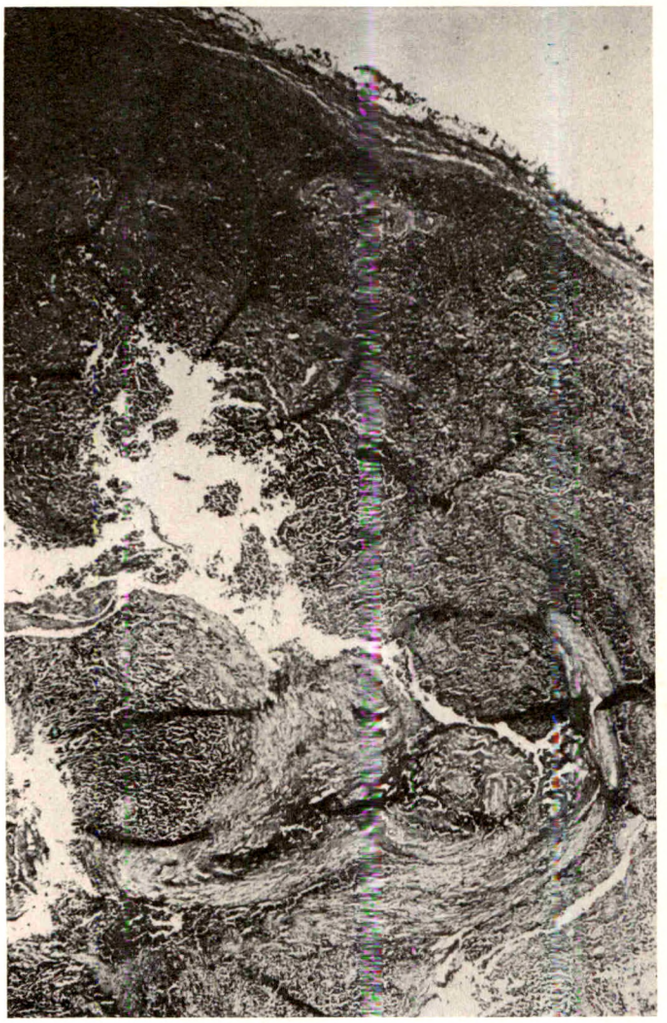


Fig. 5 (Welsh and Jhavery). Pre-auricular lymph node showing secondary malignant melanoma (hematoxylin-eosin, ×25).

*Pre-auricular lymph node*—The section of the pre-auricular lymph node shows pigmented secondary tumor cells (Figs. 5 and 6).

*Left cornea*—The cornea of the left eye that had been removed by corneal transplant showed marked hyperpigmentation of the basal cells and to a lesser extent in the prickle cells. There was no indication of junctional nevus or melanoma in the sections (Fig. 7).

## Discussion

In the case presented here, a malignant melanoma involving the cornea was thought to have arisen primarily from the cornea, but extension from a small limbal melanoma could not be excluded since serial sections were not taken. Clinically, the melanoma appeared to be corneal. Reese[5] reports on 10 cases described by von Hippel and says that some of these cases may have been malignant melanomata extending from the limbus. Hogan and Zimmerman[6] state that primary malignant melanomata of the limbus and of the cornea are very similar. In African patients, there is normally increased limbal pigmentation, and superficial pigmentation can extend onto the surface of the cornea. Occasionally, small areas of superficial pigmentation occur in areas of superficial keratitis or trauma. Michaelson[7] has produced pigment-cell proliferation from the limbus to the cornea experimentally in the rabbit. One

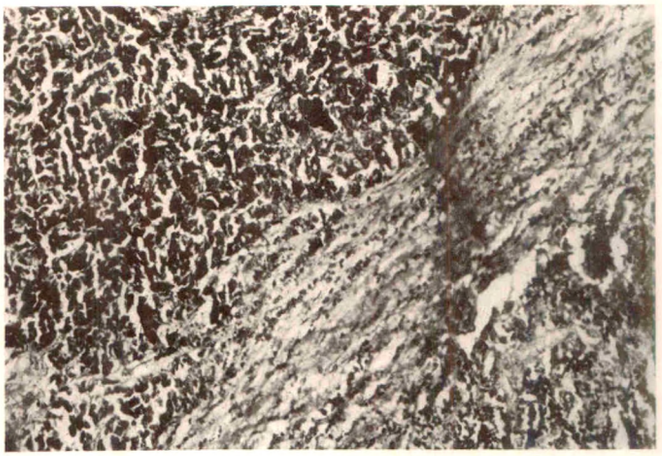


Fig. 6 (Welsh and Jhavery). Secondary malignant melanoma cells from pre-auricular lymph node (hematoxylin-eosin, ×150).

would have supposed that there would be an increased tendency for pigmented races to develop melanomata of the limbus and cornea, but this is not so in our experience. The appearance of the cornea of the left eye was abnormal and unusual. Pigmentation of the basal cells appeared to be the primary lesion and although no junctional activity was present, it is tempting to suggest that this could arise in the future and that originally the right eye presented a similar appearance.

The appearances of the tumor fit with previous descriptions and superficial vascularization is a prominent feature. It invaded Bowman's membrane, which is not characteristic.[6] Stallard's case[2] also destroyed most of Bowman's membrane, corneal epithelium, and bulbar conjunctiva, and had infiltrated the substantia propria of the cornea. He mentions one case report by François, Gildemyn, and Rabaey in which the authors considered the neoplasm to be slowly penetrating and a partial keratectomy was performed.

The subsequent metastasis of the tumor also invites comment. Following the enucleation, since the conjunctiva looked normal and the pathologic report was that of a malignant melanoma of the cornea, exenteration was not contemplated.

When the patient returned on June 10, 1969, there was extensive involvement of the conjunctiva with secondary extension to the parotid and submaxillary lymph nodes. Last[8] says that the cornea has no lymphatic drainage, and that the conjunctiva has a lymphatic drainage that drains to the parotid glands from the lateral side and to the submandibular glands from the medial side. The secondary deposits are thus derived from the con-

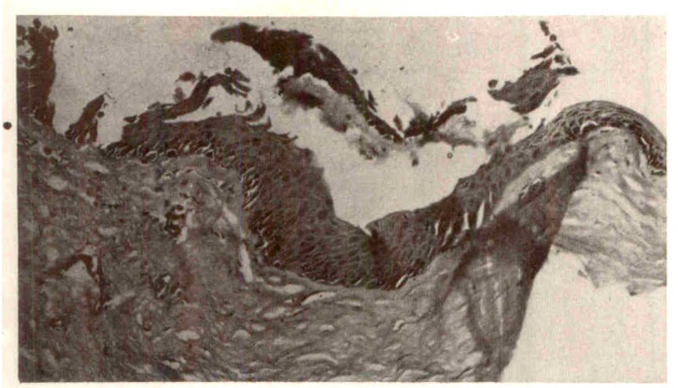


Fig. 7 (Welsh and Jhavery). Hyperpigmentation of basal cells and prickle cells of left cornea (hematoxylin-eosin, ×300).



Fig. 8 (Welsh and Jhavery). Photograph showing present appearance of right orbit 18 months after exenteration. Tissue at apex is skin graft. Left eye shows corneal graft.

junctiva and not from the cornea. The orbital contents were exenterated and microscopic examination revealed no extension of melanoma deep to the conjunctiva. It is interesting to note that conjunctival involvement from the cornea took at least 18 months to develop. By January 12, 1971, there had been no orbital recurrence (Fig. 8), with no further evident lymphatic extension, indicating the slow rate of general systemic involvement.

## Summary

A malignant melanoma of the cornea arose in a 23-year-old African Zulu man. The eye was enucleated, but 18 months later there was recurrence in the orbit, conjunctiva, and in the pre-auricular and submandibular glands. The fellow cornea showed irregularity of the superficial layers with pigmentation and thinning. The tumor was thought to have arisen primarily from the cornea, but extension from a small cornea sclerolimbal melanoma could not be excluded histologically.

## Acknowledgments

I thank Professor L. Baker Head, Department of Surgery, and Dr. H. Wannenburg, Superintendent of King Edward VIII Hospital, for permission to publish this case. I also thank Professor J. Wainwright, of the Department of Pathology, and Mr. Stuart for the preparation of the photographs.

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# THE HISTOPATHOLOGY AND ULTRASTRUCTURE OF CONGENITAL, CENTRAL CORNEAL OPACITY

## (PETERS' ANOMALY)

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Peters' anomaly is a congenital, central corneal stromal opacity usually associated with a defect in the posterior stroma and Descemet's membrane and anterior synechiae which extend from the pupillary zone of the iris to the periphery of the corneal opacification.[1-3] Glaucoma is commonly associated with this condition. Less frequent associations are anterior polar cataracts or other forms of congenital cataracts, and it is not infrequently associated with microphthalmus and sclerocornea.[3] Eighty percent of the reported cases of Peters' anomaly are bilateral. Because it may coexist with other developmental anomalies of the anterior segment, i.e., mesodermal dysgenesis of the iris and posterior embryotoxin, it has been suggested by Reese and Ellsworth[4] that these anomalies be classified into a single group and called the anterior chamber cleavage syndrome.

Peters' anomaly was first considered to be caused by an intrauterine infection.[5] At present, it is generally believed to be a developmental anomaly that is caused by either a delayed separation of the lens vesicle,[6] or a primary disorder in the development of the endothelium of the anterior chamber,[7] or a combination of both of these.

Recently, one of us (S.I.B.) reported the successful transplantation of one cornea of a ten-month-old infant with Peters' anomaly.[8] The eye that received the corneal graft had adhesions of the central iris to the cornea, in addition to an anterior polar cataract that was also adherent to the back of the cornea. At surgery, it was apparent that the anterior layer of the iris was underdeveloped, indicating that in addition to Peters' anomaly, there was an additional component of mesodermal dysgenesis of the iris. Preliminary histologic examination of the excised host cornea indicated that in the zone of the opacification, the endothelium, Descemet's membrane, and Bowman's membrane were absent.[8] The second cornea of this patient was grafted and the histologic description and ultrastructure of both specimens are presented in this report.

### MATERIALS AND METHODS

The second corneal specimen was a corneal disk 7 mm in diameter removed during corneal transplantation of the right eye of a 20-month-old baby girl. During surgery, iris adhesions to the peripheral temporal portion of the opacification were removed with sharp dissection, leaving the iris grossly intact with the pupil responsive to mydriatics. The donor cornea was sutured to the host cornea as reported with the left eye. The sutures were removed after four months and the graft has remained transparent to the present time. Visual psychological testing performed at the New York Lighthouse for the Blind indicated that the child could perform visual tasks equal to those of children in her age group with normal vision.

The corneal specimens were fixed in 3% glutaraldehyde in 0.2M sodium cacodylate buffer (pH 7.4) and post-fixed with 2% osmium tetroxide in 0.2M sodium cacodylate and embedded in Epon. Thick sections of the epoxy-embedded tissue were stained with basic fuschin and alkalinized methylene blue and examined with the light microscope. Thin sections were cut with a LKB-3 micro-

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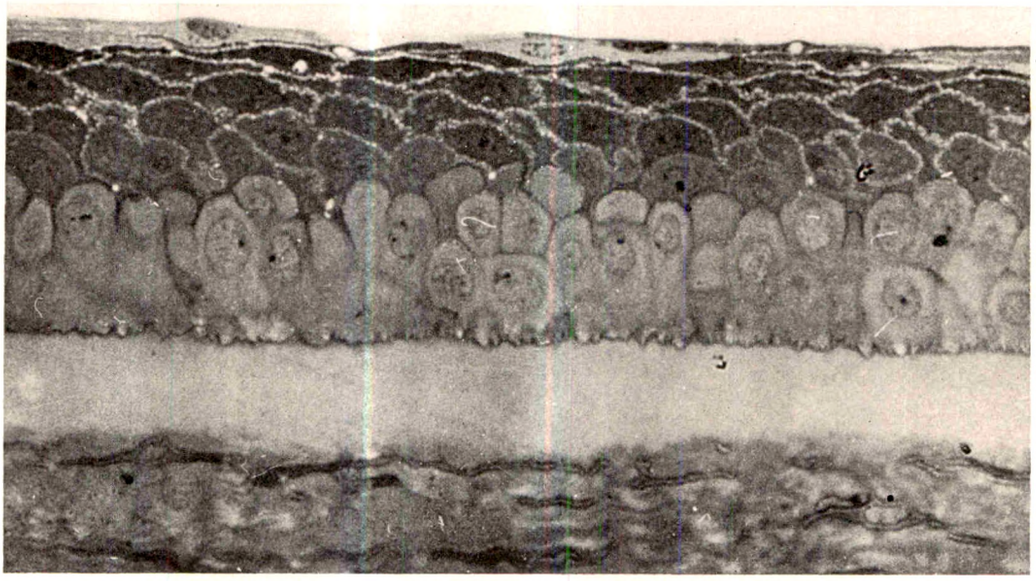


Fig. 1 (Nakanishi and Brown). Section of the peripheral portion of excised cornea showing a normal appearing Bowman's membrane (basic fuchsin and alkalinized methylene blue, ×400).

tome with a diamond knife, mounted on uncoated copper grids, stained with uranyl acetate and lead citrate, and examined with an AEI EM-6B at 60 kv.

## Histology

The epithelium of both specimens was of normal thickness. The basal layer appeared edematous and contained a few darkly staining cells. Bowman's membrane appeared to be of normal thickness in the periphery of both specimens (Fig. 1), thinned in the midperiphery (Fig. 2) in the first cornea, and was absent in the central 3-4 mm of both specimens (Figs. 3 and 4). The left cornea contained many blood vessels throughout the stroma. The right cornea was avascular. The architecture and cells of the peripheral stroma of both specimens appeared normal. However, in the more central area, there was an increased number of stromal cells in the subepithelial zone where Bowman's membrane was absent. The endothelium and Descemet's membrane were present in the pe-

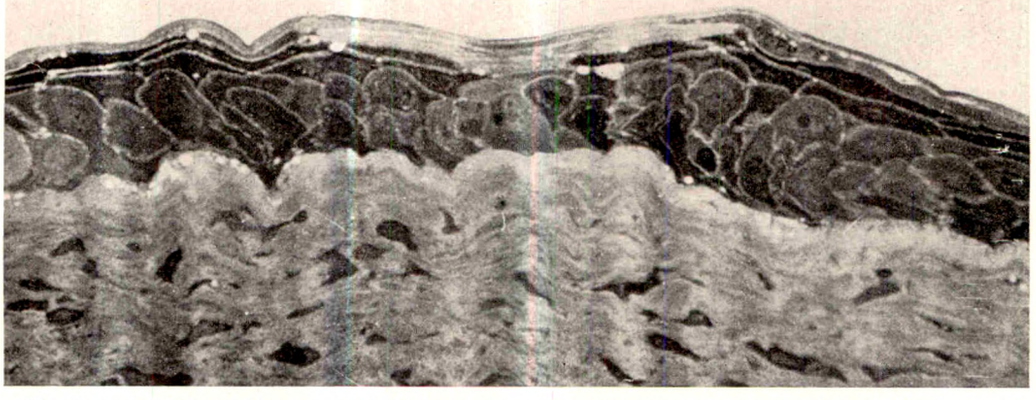


Fig. 2 (Nakanishi and Brown). Midperiphery of specimen from first eye showing thinning of Bowman's membrane (basic fuchsin and alkalinized methylene blue, ×400).

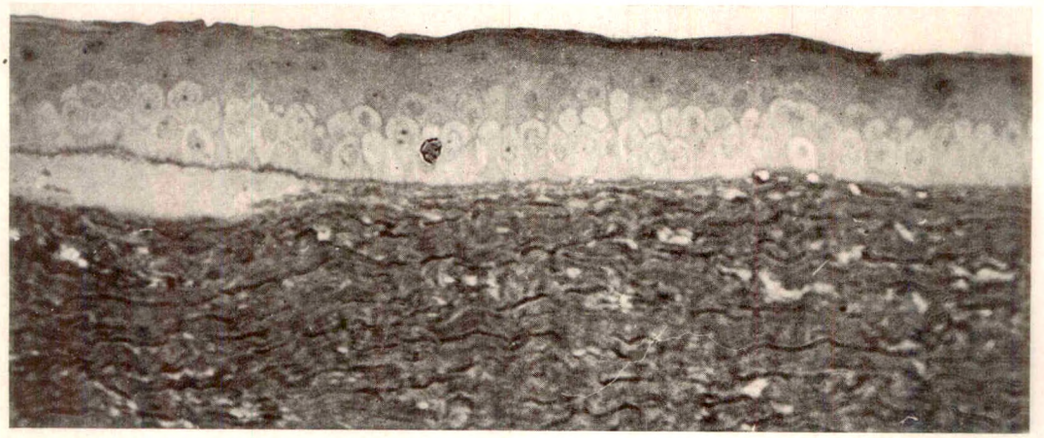


Fig. 3 (Nakanishi and Brown). Midperiphery of specimen from second cornea showing where Bowman's membrane tapers and stops (basic fuchsin and alkalinized methylene blue, ×400).

riphery of both specimens (Fig. 5). Descemet's membrane thinned in the midperiphery and disappeared behind a retrocorneal membrane of loose connective tissue (Fig. 6). The central endothelium appeared to be absent in the first and present in the second specimen.

### Electron microscopy

The anterior epithelial cell layers appeared normal except for fewer tonofilaments. The nuclei of the basal cells were usually in the anterior half of the cells. The basal portion of the basal cells projected deeply and irregularly into the stroma (Fig. 7). The basement membrane of the epithelium was well developed and generally intact throughout both specimens.

The peripheral portions of the Bowman's membrane appeared to have a normal thickness and configuration, except that it was absent immediately posterior to the basement membrane. Instead, there were fine, closely-packed fibrils that were particularly promi-

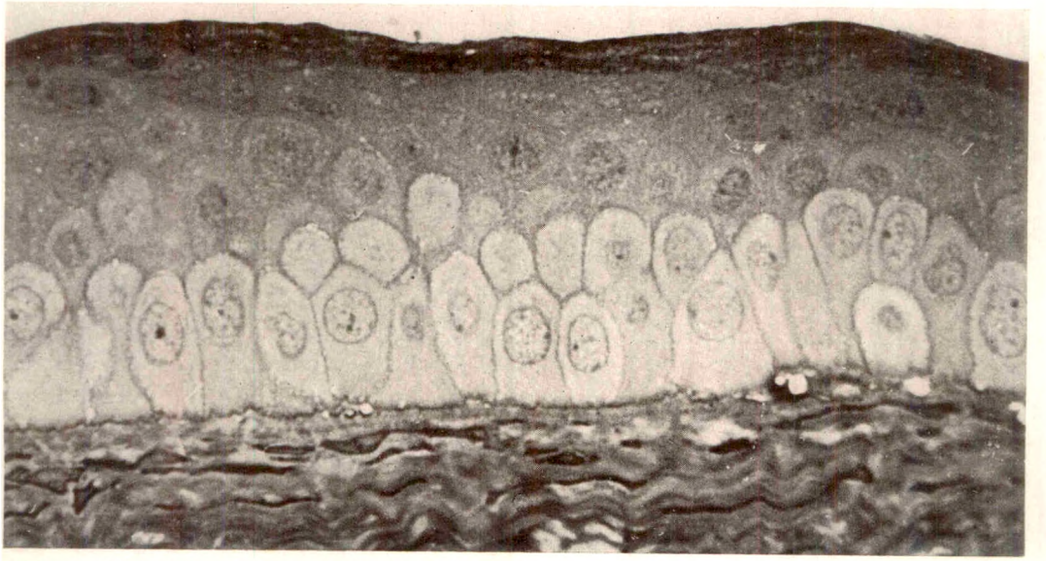


Fig. 4 (Nakanishi and Brown). Section of central cornea showing absence of Bowman's membrane (basic fuchsin and alkalinized methylene blue, ×400).

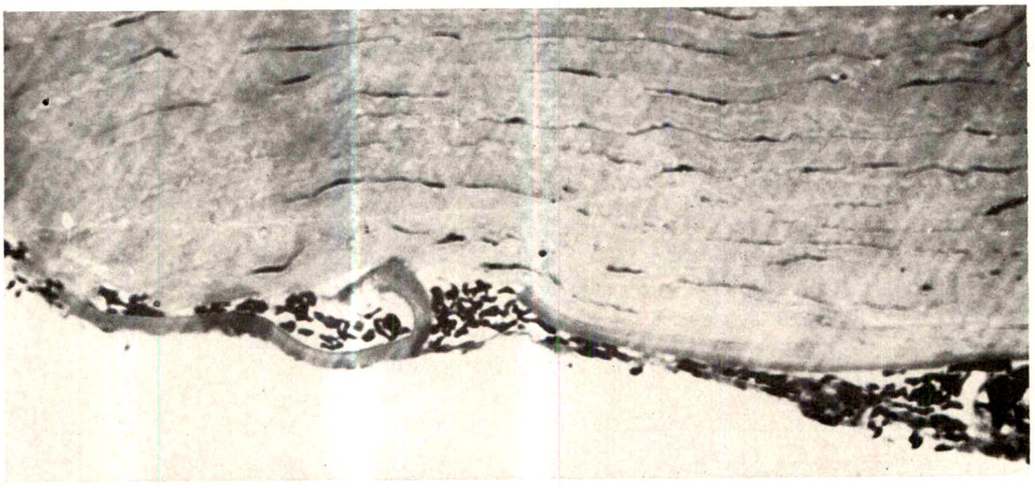


Fig. 5 (Nakanishi and Brown). Section of peripheral portion of specimen showing a normal appearing Descemet's membrane (basic fuchsin and alkalinized methylene blue, ×400).

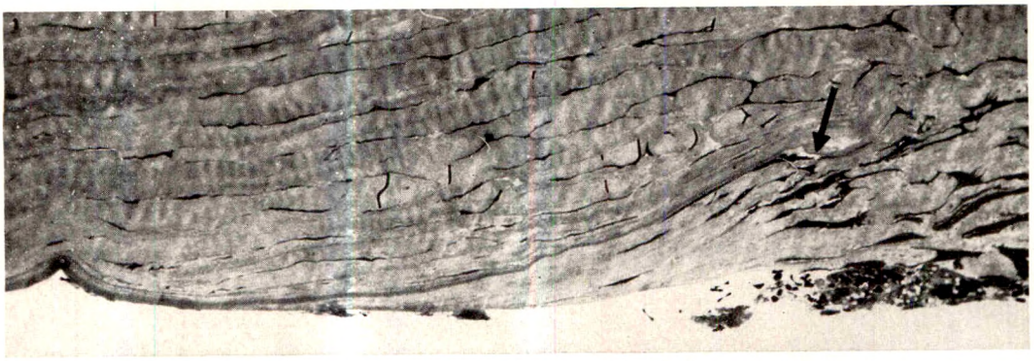
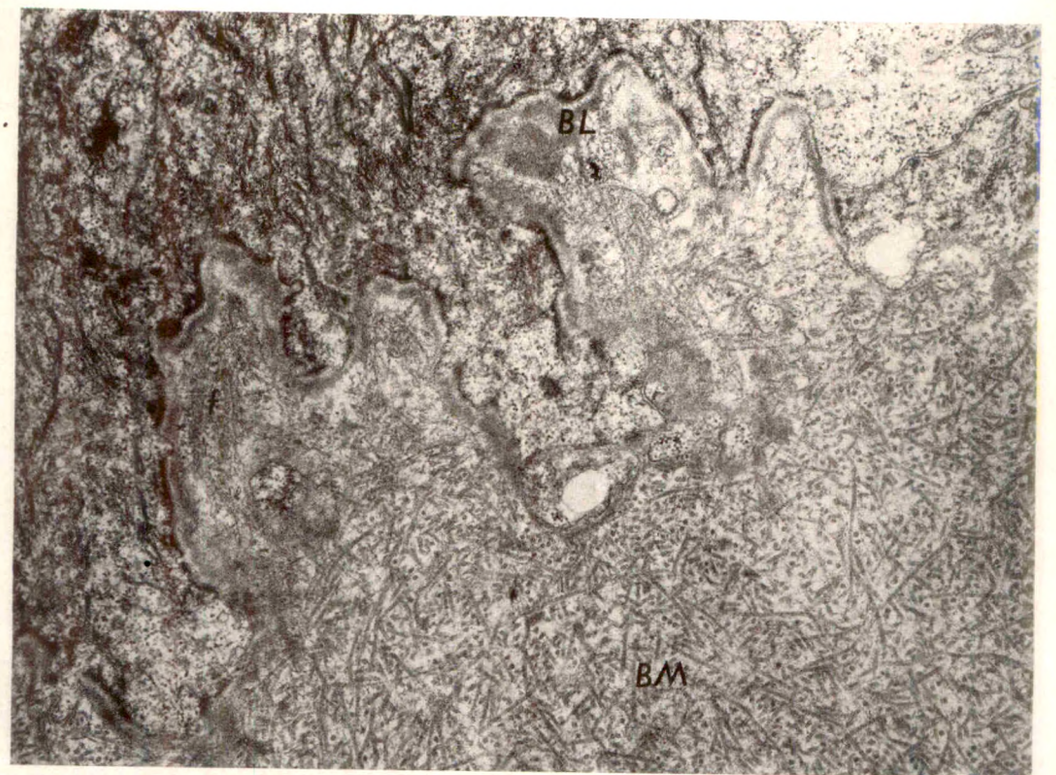


Fig. 6 (Nakanishi and Brown). Section of midperiphery of excised cornea showing Descemet's membrane thin and disappear (arrow) behind a retrocorneal membrane (basic fuchsin and alkalinized methylene blue, ×400).

Fig. 7 (Nakanishi and Brown). Electron micrograph of the epithelial-stromal junction of the peripheral portion of the excised cornea. The basal cells project irregularly and tortuously into the superficial stroma. Beneath the basement lamina, there are fine, closely-packed fibrils (f) which differ from those of Bowman's membrane (BM) (×25,000).

Fig. 8 (Nakanishi and Brown). Higher power of epithelial-stromal junction of the peripheral cornea. The fine, closely-packed fibrils beneath Bowman's membrane are more easily seen beneath the basement lamina. A portion of the fibroblast (F) is contiguous with a process of a basal epithelial cell (P) (×60,000).


BL
f
BM


F
f
P

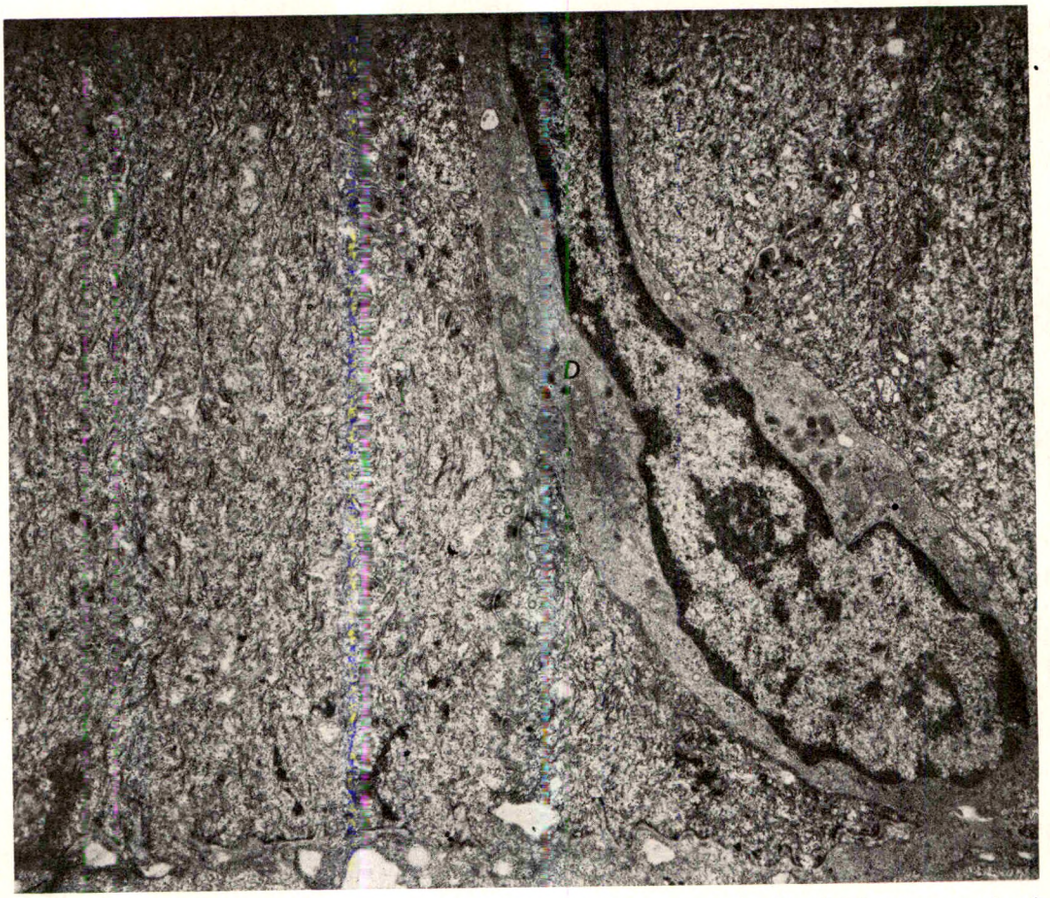



Fig. 9 (Nakanishi and Brown). An unusual cell (dendritic or polygonal cell) (D) between two basal epithelial cells (×15,000).

nent within the unfoldings of the basement membrane and basal epithelium cells (Figs. 7 and 8). An occasional dendritic type of cell was observed in the basal layer of the epithelium (Fig. 9).

In the midperiphery, the anterior portion of Bowman's membrane thinned (Fig. 10), tapered, and finally disappeared. In the central portions of both specimens, Bowman's membrane was absent (Fig. 11).

In the central anterior stroma, cytoplasmic processes of keratocytes were frequently observed to contact the basal epithelial cells through defects in the basement membrane. In the posterior central stroma, the collagen lamellae were disorganized (Fig. 12). In this area, the cytoplasm of the stromal cells were surrounded by an electron-dense amorphous material (Fig. 13).

Endothelial cells lined the posterior surface of the second specimen but were absent behind the central portion of the first specimen. In these cells, the endoplasmic reticulum though well developed were never observed to be close to the anterior cell membrane. This suggests reduced secretory activity. In the peripheral portions of the specimen, Descemet's membrane appeared to consist of a thin layer of amorphous material contiguous with the endothelial cell membrane (Fig. 14). In addition, there were strands of a similar material anterior to this

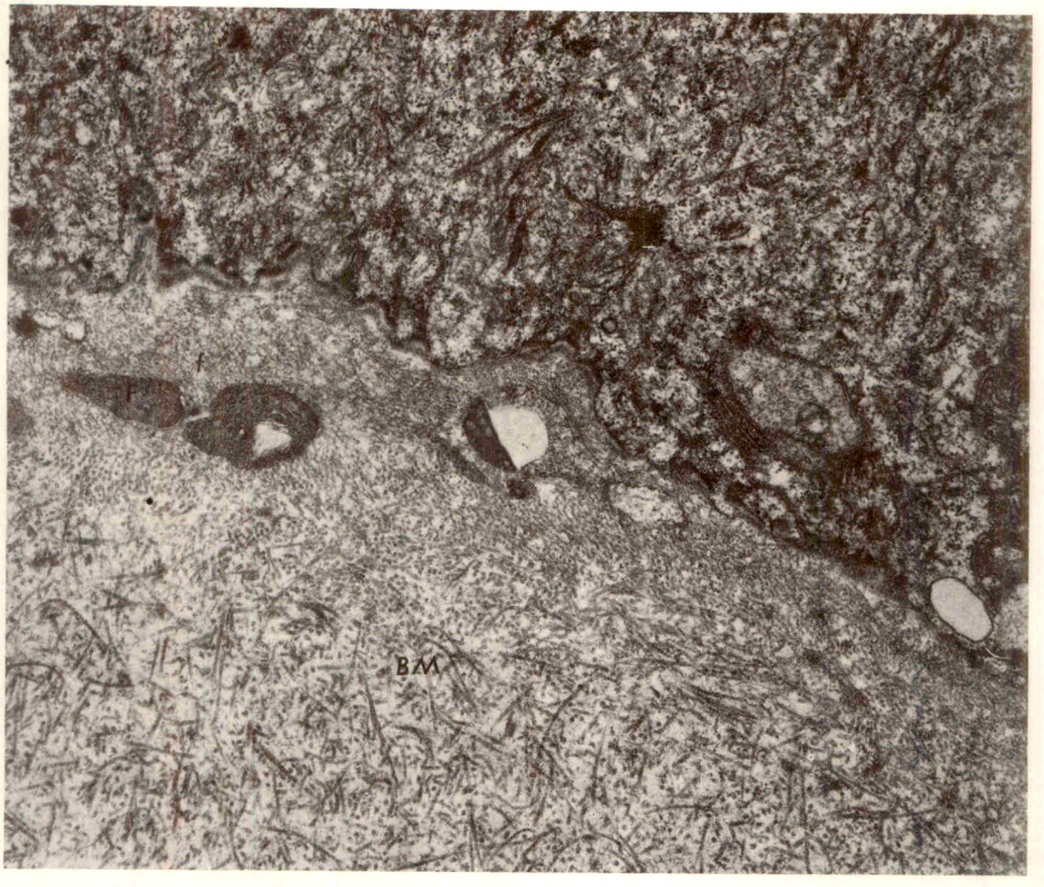



Fig. 10 (Nakanishi and Brown). Electron micrograph of the epithelial-stromal junction of the midperipheral portion of the specimen. The layer of tissue between the epithelial basement lamina and Bowman's membrane is thicker. The diameters of the fibrils (f) of this layer are also thicker. Portions of stromal cells (F) are in this layer (×30,000).

layer. Centrally, the amorphous layer was much thinner and appeared similar to the material surrounding the keratocytes in the posterior stroma (Fig. 15).

## Comment

Histologic examination of the two specimens from corneas with Peters' anomaly indicated that both Bowman's membrane and Descemet's membrane were intact and had apparently normal thicknesses in the periphery of the specimens. In the midperiphery, these layers gradually thinned and were absent in the most central portions of both specimens. The central stroma was unusual in that anteriorly there were many keratocytes and posteriorly there was a retrocorneal connective tissue membrane. This retrocorneal membrane was localized and filled the area where a defect in the stroma is usually found in Peters' anomaly.

Electron microscopy showed that the peripheral portions of both Bowman's membrane and Descemet's membrane were abnormal. Bowman's membrane was absent immediately beneath the epithelial basement membrane.

The appearance of Descemet's membrane in the periphery of the specimens was similar to the Descemet's membrane secreted by

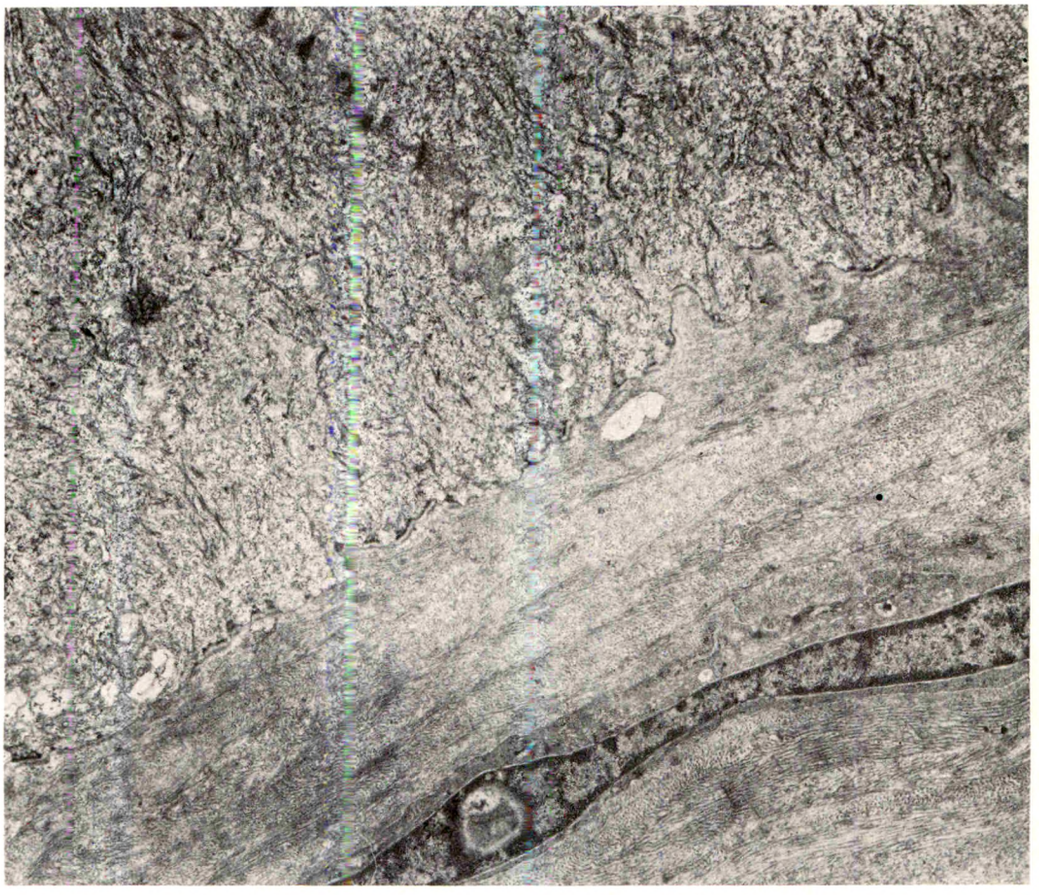


Fig. 11 (Nakanishi and Brown). Electron micrograph of the epithelial-stromal junction of the central portion of the excised cornea showing complete absence of Bowman's membrane (×15,500).

endothelial cells that have spread behind a two- to three-week-old wound.[8] The electron dense amorphous material contiguous with the cell membrane of the endothelial cells in the midperiphery was similar to newly secreted Descemet's membrane in a three-day old wound.[9] This immaturity of Descemet's membrane is difficult to explain because the specimens were from one- and two-year-old infants.

Amorphous electron dense material which resembled the presumed immature Descemet's membrane surrounded cells in the posterior central stroma. These cells probably represent aberrant endothelial cells. Similar cells were observed in studies of the wounds of grafted corneas.[9]

These studies of Peters' anomaly show that in addition to the usual defect in the central portion of Descemet's membrane, there was also an absence of Bowman's membrane in the central portion of both specimens. Recent studies by Hay and Ravel[10] indicate that the epithelium is responsible for the embryogenesis of Bowman's membrane. If this is true, Peters' anomaly is an ectodermal alteration in addition to the generally recognized mesodermal dysgenesis. We contend that the grouping by Reese and Elsworth[4] of many of the developmental anomalies of the struc-

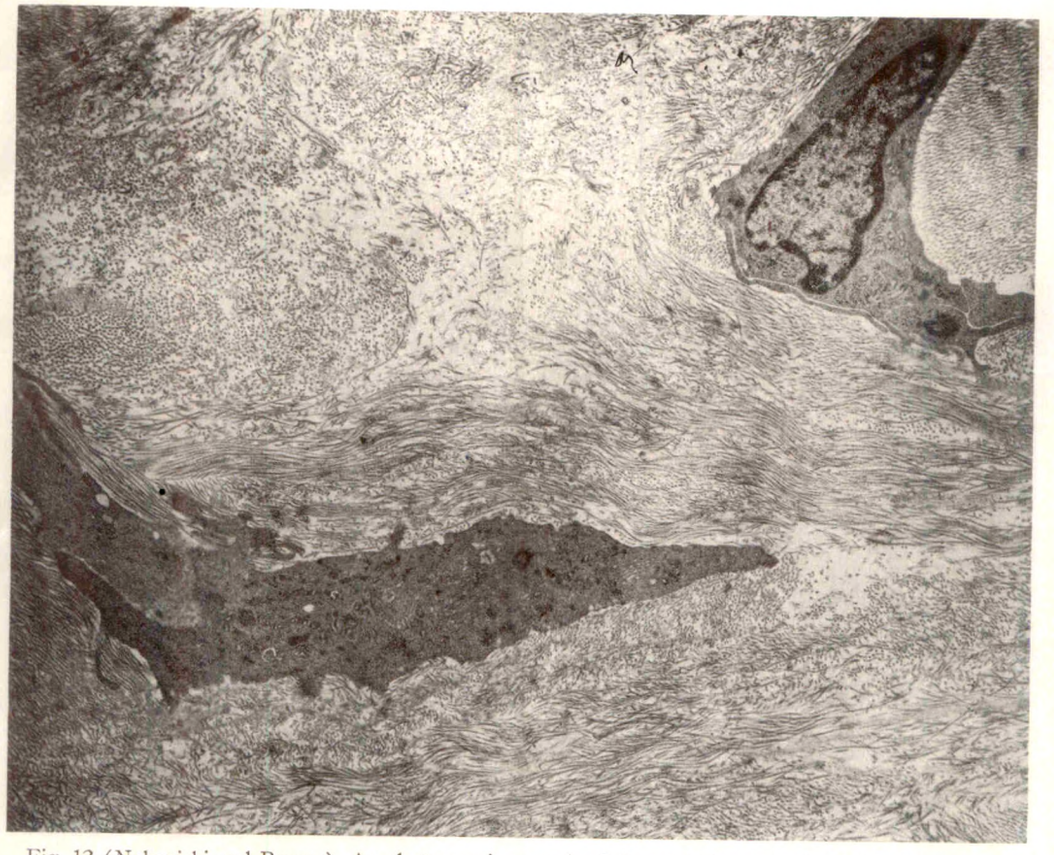


Fig. 12 (Nakanishi and Brown). An electron micrograph of the posterior central stroma showing a cell surrounded by a thin, amorphous, electron-dense layer (×25,000).

tures bordering the anterior chamber under one classification is a useful contribution. However, the absence of Bowman's membrane in the cornea of Peters' anomaly indicates that, as Alkemade[3] recently suggested, the name anterior chamber cleavage syndrome is embryologically incorrect, i.e., the portions of cornea that are altered in Peters' anomaly do not normally develop during the formation of the anterior chamber.

## Summary

Histologic examination of two corneas with Peters' anomaly showed that in addition to the usual absence of a central portion of Descemet's membrane, Bowman's membrane was also absent in the central portion of both specimens. The peripheral portions of both Bowman's and Descemet's membrane appeared to be of normal thickness. Electron microscopy showed that the peripheral portions were separated from the epithelium by a thin layer of fibrous tissue and that the peripheral portions of Descemet's membrane were separated into lamellae.

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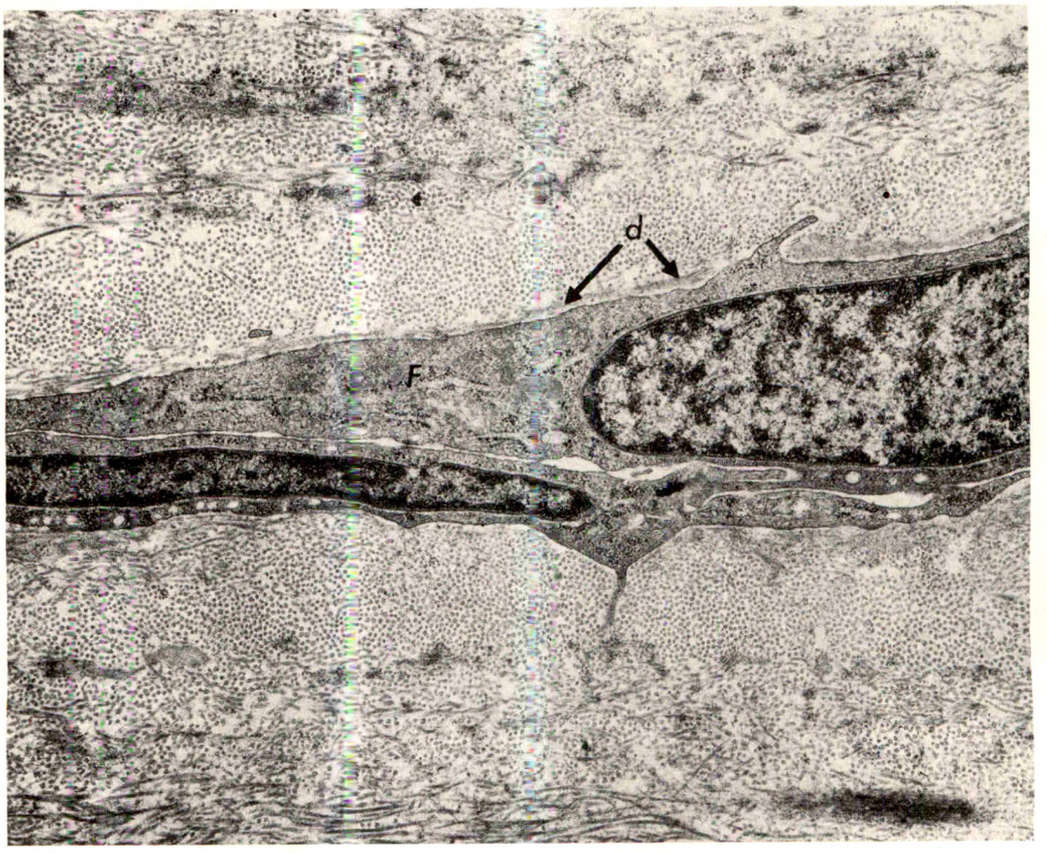



Fig. 13 (Nakanishi and Brown). An electron micrograph of the posterior central stroma showing a cell (F) surrounded by a thin, amorphous, electron dense layer (d) (×25,000).

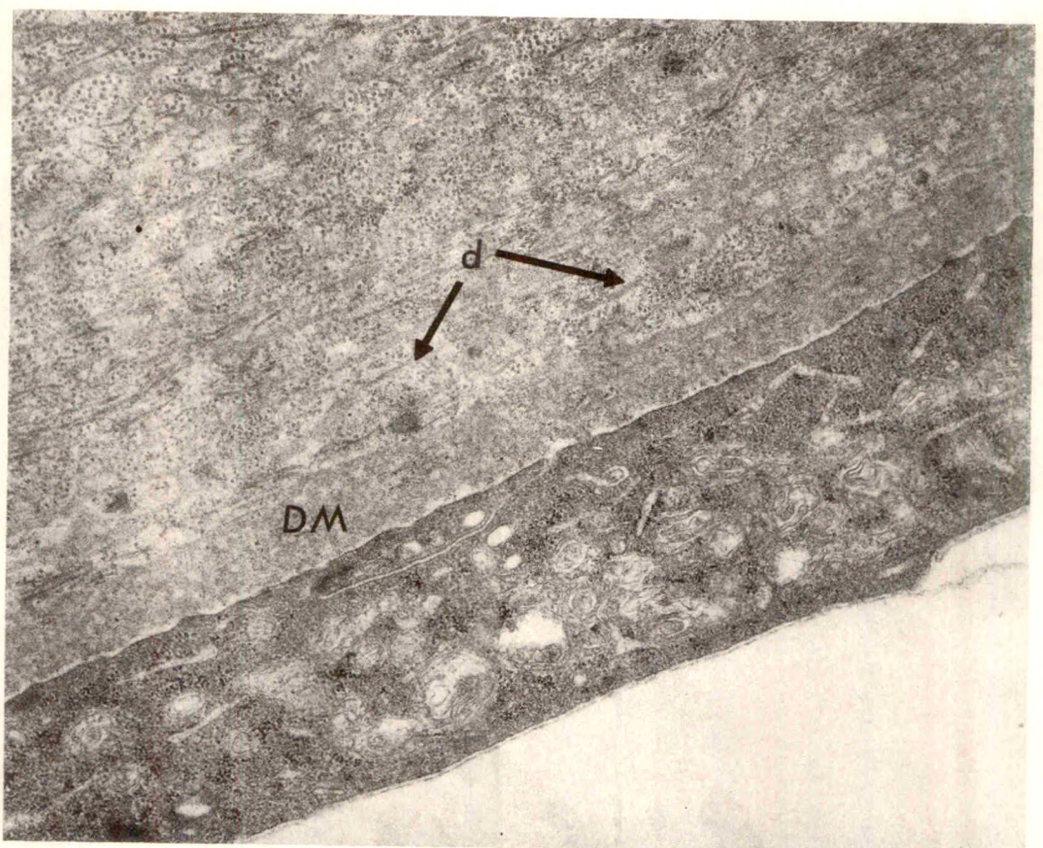



Fig. 14 (Nakanishi and Brown). An electron micrograph of the endothelium and the overlying Descemet's membrane. Descemet's membrane (DM) appears to be made up of a thin layer adjacent to the endothelium and additional loose strands of a similar material (d) in the stroma anterior to the thin layer (×25,000).

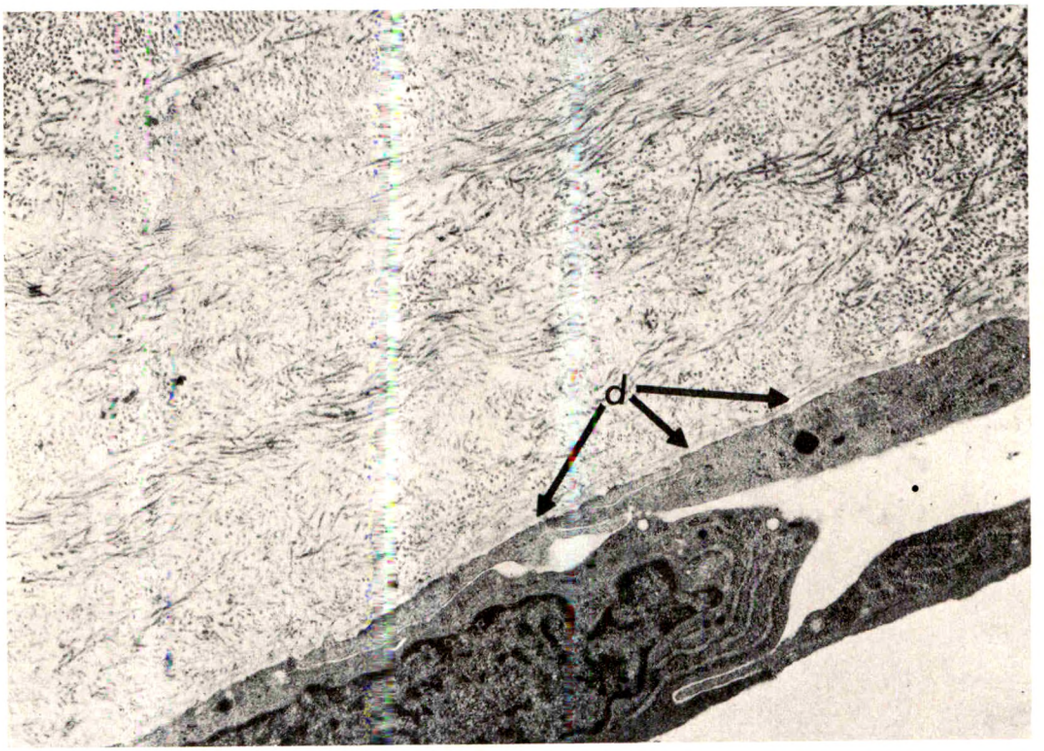



Fig. 15 (Nakanishi and Brown). Electron micrograph of posterior central cornea showing an endothelial cell with a thin basement membrane-like material (d) contiguous with the external cell membrane (×12,500).

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# REPORT OF A CASE OF NOCARDIA ASTEROIDES KERATITIS

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AND ARTHUR C. ELLISON, M.S.
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Ocular infection caused by Nocardia asteroides is rare. External infections have been reported infrequently,[1-4] but more recent reports deal with intraocular endogenous infection.[5-6]

This organism is a Gram-positive, filamentous bacterium classified in the order Actinomycetales and sensitive to antibacterial treatment. However, frequently it is described as a fungus.[3,4,7,8] It is important to recognize the characteristics of Nocardia keratitis so that adequate treatment can be initiated. Ths case report describes a Nocardia corneal ulcer in a patient treated with antiviral agents and corticosteroids. The effect of topical corticosteroids upon experimentally induced infection was studied.

## CASE REPORT

A six-year-old boy was struck in the right eye with a "dirt ball." Particles of dirt were removed from the eye by irrigation, and within 24 hours it showed no signs of irritation. Three weeks later, however, the eye became inflamed and oxytetracycline (Terramycin) ophthalmic ointment was then applied for several days without improvement. The patient was referred to an ophthalmologist who found a corneal lesion and prescribed chloramphenicol ointment and topical corticosteroids, but the infection became progressively worse. Another ophthalmologist treated the boy with sulfacetamide and 5-iodo-2-deoxyuridine for several days without improvement. The patient was referred to the University Eye Clinic. The child's visual acuity in the affected eye was counting fingers. His left eye was normal and he was otherwise healthy. There was right corneal edema and infiltration about 5 mm in diameter which extended from the temporal limbus to the pupillary margin. The epithelium was absent centrally and thickened at the margin of the lesion. There were multiple infiltrates, some of them expanding in a branched fashion. Peripheral deep neovascularization extended 4 mm into the cornea

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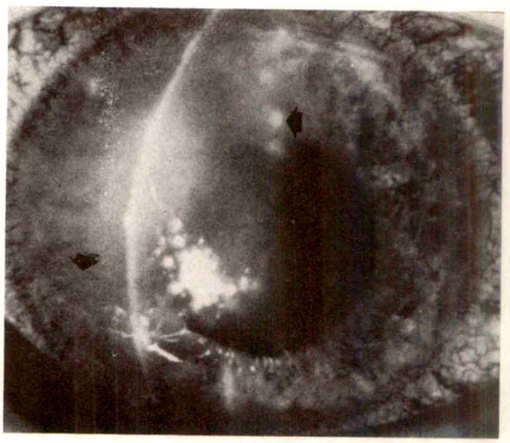


Fig. 1 (Newmark, Polack, and Ellison). Nocardia asteroides keratitis. Arrows indicate multiple infiltrates at the advancing edge of the corneal lesion and mid-stromal corneal vascularization.

(Fig. 1). The anterior chamber showed a mild inflammatory reaction.

Gram and Giemsa stains of corneal scrapings for fungus, and a potassium hydroxide wet preparation, did not reveal bacteria or fungi. Three days after plating cultures, minute mealy white colonies appeared along the culture streak on the blood-agar plate. The organism was a Gram-positive and acid-fast filamentous bacterium identified as Nocardia asteroides (Fig. 2), sensitive to sulfonamides, tetracycline, and penicillin. The patient was treated with sulfadiazine systemically, sulfacetamide 30% every two hours, and tetracycline in oil, 1%, every two hours topically, alternating with sulfacetamide. Similar white mealy colonies grew also on the Sabouraud's medium five days after inoculation. Systemic therapy was discontinued after approximately three weeks of treatment. At this time, the corneal lesion was healed (Fig. 3), and the patient's right vision was 20/25 without correction.

## EXPERIMENTAL STUDY

The possibility that Nocardia infection of the cornea could be aggravated by corticosteroid treatment was investigated in rabbit eyes. The corneas of 12 pigmented rabbits were inoculated intralamellarly with a diluted suspension of Nocardia asteroides filaments (isolated from the patient described). Corneal infiltrates were noted within three days. Six rabbits were treated with normal saline

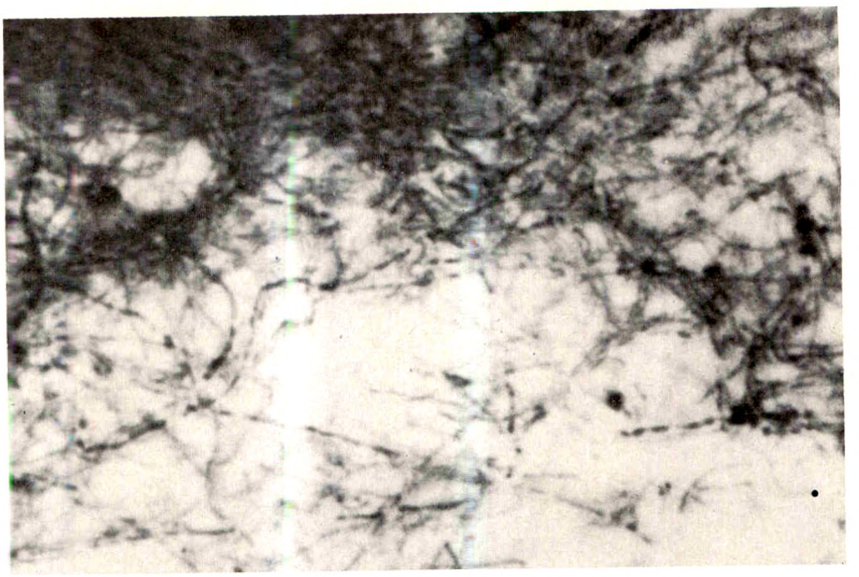


Fig. 2 (Newmark, Polack, and Ellison). Nocardia asteroides from blood-agar culture. Note the filaments with fragmentations into bacteria-like particles (Gram stain, ×1000).

solution drops four times daily, and six rabbits were treated with instillations of dexamethasone ophthalmic solution 0.1% four times daily for a three-week period.

Rabbit corneas treated with the corticosteroid developed large granulomatous lesions (Fig. 4) with extension into the anterior chamber in two animals. The saline-treated eyes showed small lesions which eventually healed by vascularization. Even though the corticosteroid-treated group showed large corneal granulomas, the eyes showed minimal intraocular reaction, except in the two cases of anterior chamber extension.

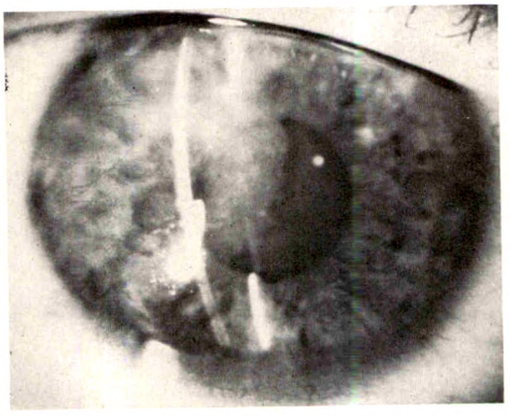


Fig. 3 (Newmark, Polack, and Ellison). Appearance of the cornea four weeks after sulfacetamide and tetracycline treatment.

## Discussion

The Actinomycetales are filamentous bacteria related to the Mycobacteria, while superficially resembling fungi. In tissue culture, they grow in branched fashion with fragmentations into bacteria-like particles. The genus Nocardia is aerobic and has narrow, Gram-negative, acid-fast bacillary or coccal forms. These forms grow best in blood-agar, but also on simpler media, producing white colonies with a dry and crumbly appearance. Nocardia is usually sensitive to sulfadiazine and frequently to tetracycline and penicillin; however, in vitro tests are warranted to determine the sensitivity of each new strain.

The corneal lesion seen in this patient was not unlike that caused by atypical Mycobacteria[9-10] or mycotic infections. The history and the aggravation caused by topical corticosteroids suggested a mycotic lesion; however, it is unusual for a fungal ulcer to show minimal or absent ocular inflammation. The corneal scrapings were not stained for acid-fast organisms, but with this type of corneal lesion, particularly when no bacteria or fungus was found, this should have been done. It is interesting that this patient was initially treated with appropriate medications, but not frequently enough.

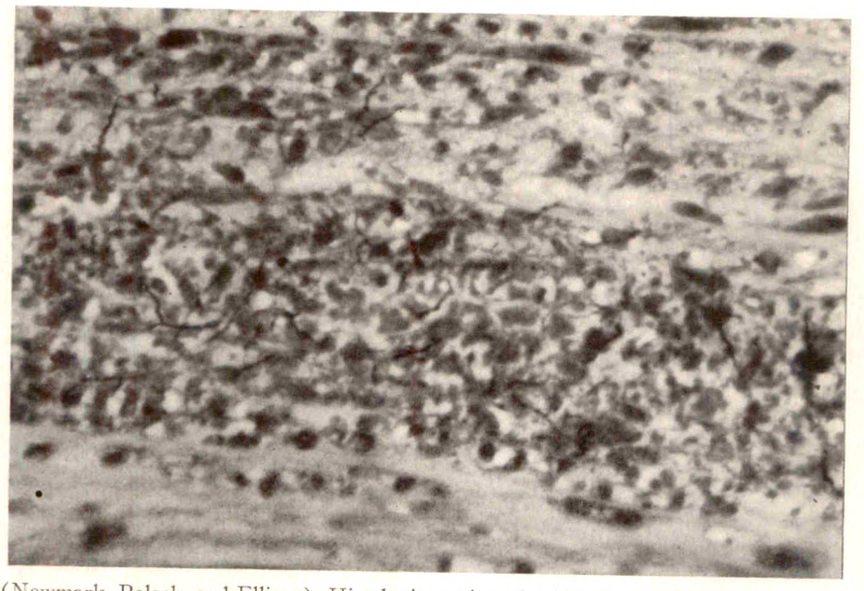


Fig. 4 (Newmark, Polack, and Ellison). Histologic section of rabbit cornea showing Nocardia asteroides (arrows) within the granulomatous lesion (Ziehl-Neelsen, ×400).

It is well known that corticosteroids aggravate bacterial and fungal infections, and this also is true for this type of infection, as substantiated by the rabbit experiment reported. Experimental corneal infection by Nocardia, as reported by others[1,11] and confirmed by us, causes corneal granulomata with ocular inflammation and heals by vascularization. When corticosteroids are used, the corneal infection is much more severe, and bacterial extension into the anterior chamber may occur.

## Summary

Corneal infection due to Nocardia asteroides developed in a six-year old boy who was initially treated with antibiotics, corticosteroids, and antiviral agents. Once the organism was identified, the keratitis responded to therapy with topical and systemic sulfonamides and topical tetracycline. Experimental infections in rabbit eyes showed that granulomatous nocardial corneal lesions regress spontaneously by vascularization with almost no intraocular inflammation, but instillation of topical corticosteroids aggravates the infection.

## Acknowledgments

Mr. Al Foxworth supplied technical assistance. The photographer was Mr. Jerry Sewell. The animals used in the study were maintained in animal care facilities fully approved by the American Association for Accreditation of Laboratory Animal Care.

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# TESTING FOR CONGENITAL SYPHILIS IN INTERSTITIAL KERATITIS

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The presence of viable and virulent Treponema pallidum in the human eye in congenital syphilis despite massive doses of penicillin has recently been proven by Hardy and associates.[1] Furthermore, the incidence of congenital syphilis in children under 10 years of age in the United States rose by 168% in the past decade.[2] Since it is known that 90% of cases of interstitial keratitis are due to congenital syphilis,[3] this review of interstitial keratitis with emphasis on the serum FTA-ABS test is presented.

## Materials and Methods

Cases of interstitial keratitis personally examined at the Bascom Palmer Eye Institute between 1963-70 were reviewed. Only those showing typical biomicroscope signs of syphilitic interstitial keratitis were accepted. These signs were: the presence of deep stromal opacifications, often patchy or feathery in outline, usually seen with a silvery sheen reflex just in front of Descemet's membrane, and accompanied by the presence of ghost vessels seen by direct or retroillumination in both eyes. Unilateral cases and those not confirmed by external ocular photographs were excluded to preclude inclusion of other forms of corneal disease in the study group. Twenty patients fulfilled these criteria, and their records were reviewed for the following data: age, sex, history of ocular inflammation in childhood, family history suggestive of syphilis, right eye vision, left eye vision, pupillary findings (with emphasis on the presence of light-near dissociation), presence of glaucoma, visual field defects, ophthalmoscopic appearance of the optic nerve, presence or absence of chorioretinitis, deafness, stigmata, findings of aqueous humor paracentesis, serum VDRL, and serum FTA-ABS findings. The data are summarized in Table 1.

*Findings*—There were five males and 15 females in this series. This 3:1 ratio of higher incidence of interstitial keratitis in females has been noted in previous studies.[4] The age range was nine to 70 years, with a median age of 49 and a mean age of 53 years. This finding was consistent with the fact that the patients were for the most part adults referred for neuro-ophthalmologic consultation. There were only two patients with acute attacks of interstitial keratitis in the group, and these were the two youngest in the series (females aged nine and 22 years). The patients in this study were thus typical of cases of late interstitial keratitis when the diagnosis is made at routine slit-lamp examination of eye clinic patients. A history of ocular inflammation in childhood, usually lasting for many months, was easily elicited in 15 of the 20 patients, or 75%. While some elderly patients may not recall this history, it is usually present and is helpful in the differential diagnosis. Three patients stated that the attacks were considered to be scarlet fever, recurrent streptococcal sore throats, or rheumatic fever in childhood. The visual acuity was 20/50 or better in one eye in 15 cases, or 75%. The visual acuity was 20/200 or worse in one eye in 12 cases, or 60%. The visual acuity was markedly asymmetric in the two eyes in eight patients, or 40%. Two patients had surgical anophthalmos as a consequence of the disease, and only one patient had legal blindness in both eyes. It is known that 70% of patients with interstitial keratitis will recover at least 20/60 vision during the natural course of the disease.[3] This group therefore

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TABLE 1

DATA FROM 20 PATIENTS WITH INTERSTITIAL KERATITIS

| Case No., Age, and Sex | Childhood Ocular Inflammation | Family History | Visual Acuity | | Pupillary Findings | Glaucoma | Visual Fields | Fundus Findings | Deafness | Stigmata | Aqueous Findings* | Serology* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | RE | LE | | | | | | | | VDRL | FTA-ABS |
| 1. 52-F | + | + | 20/50 | 20/50 | Normal | No | — | Chorioretinitis | Yes | Yes | | NR | NR |
| 2. 46-M | + | + | 20/30 | 5/200 | Normal | Yes | Contracted | Normal | No | — | | NR | R 2+ |
| 3. 49-F† | + | + | 20/100 | 20/200 | LND‡ | No | Abnormal | Normal | +− | — | | NR | +− |
| 4. 33-F | − | − | 20/20 | 20/20 | Normal | No | — | Normal | No | No | | NR | +− |
| 5. 57-F | + | − | 20/200 | 20/400 | LND† | No | Abnormal | Chorioretinitis | No | — | FA− | NR | NR§ |
| 6. 53-F | + | − | 20/60 | 20/200 | — | No | Abnormal | Chorioretinitis | No | No | | | |
| 7. 58-F | + | − | Anophthalmia | 20/60 | Normal | No | — | (equivocal) | No | Yes | | NR | R 2−3+ |
| 8. 34-M | + | + | 20/200 | 20/40 | Normal | No | Abnormal | Chorioretinitis | No | Yes | DF− | R(4) | R |
| 9. 70-F | − | + | 20/20 | 20/200 | Normal | No | Normal | Chorioretinitis | Yes | Yes | | NR | R 2+ |
| 10. 65-F | − | − | 20/40 | Anophthalmia | Normal | Yes | Normal | Normal | No | No | | NR | +− |
| 11. 33-M | − | + | 20/15 | 20/20 | Normal | No | Normal | Chorioretinitis | Yes | Yes | DF+ | NR | NR |
| 12. 65-M | + | + | 20/15 | 20/25 | Normal | Yes | Abnormal | NR | No | No | FA− | WR | +− |
| 13. 49-F | + | + | 20/60 | 20/40 | Anisocoria | No | Normal | Normal | No | Yes | DF+ | NR | R 3−4+ |
| 14. 57-F | + | − | 2/200 | 20/50 | — | No | — | Chorioretinitis | No | No | | WR† | |
| 15. 57-M | − | − | 20/20 | 20/400 | Normal | No | Normal | Retinitis pigmentosa type change | Yes | No | | WR | NR |
| 16. 63-F | + | − | 20/20 | 20/50 | Normal | No | Normal | | No | Yes | DF+ | NR | R, NR |
| 17. 43-F | + | − | 20/400 | 20/200 | LND‡ | No | Ring scotoma | Abnormal | No | No | FA+ | NR | +−, R1+ |
| 18. 9-F | + | − | HM | 20/50 | — | Yes | — | — | No | No | | NR | NR |
| 19. 22-F | + | − | 20/100 | 20/50 | Normal | Yes | — | Normal | No | — | | R | R |
| 20. 68-F | + | + | 20/70 | 20/50 | Anisocoria | No | Normal | Chorioretinitis | No | Yes | | NR | NR |

* Abbreviations: FA=fluorescent antibody stain for Treponema pallidum, DF=dark field, R=reactive, NR=nonreactive, WR=weakly reactive.
† Case 3 only patient with active optic neuritis; WR†=history of weak reaction.
‡ Light-near dissociation.
§ This patient was reactive for Treponema pallidum.

reflects the fact that those referred had more severe involvement of visual acuity.

The family history was of great interest. This was positive for syphilis or very suspicious in nine cases. Data was incomplete in eight cases, and family history was negative in three patients. In addition to asking about the serologic reactions, it is important to inquire about fetal wastage early in the second trimester or a history of stillborn infants in the mother of a patient with interstitial keratitis. Cassewitz law (the severity of congenital syphilis is inversely proportional to the duration of maternal syphilis) is helpful in this regard. It was seen that when a meticulous family history was taken for syphilis, this was positive in nine of 12 patients with interstitial keratitis, or 75%.

Another intersting observation made in this review was the fact that the pupillary light reactions were crisply intact in patients with late syphilitic interstitial keratitis. Anisocoria was noted in two patients. Light-near dissociation was looked for carefully in these cases, but was found in only three patients. Glaucoma was present in five cases, or 25% of the series. Criteria for this diagnosis were a history of elevated intraocular pressures on several occasions, as well as a history of miotic therapy combined with at least some ophthalmoscopic evidence of cupping of the optic disks. The visual fields were normal in seven cases, abnormal in seven others, and not adequately examined in six patients. There was thus a visual field defect in one-half of the patients studied by quantitative perimetry. Of the seven cases of interstitial keratitis with field defects, central scotomas were found in three; peripheral wedge-shaped optic nerve-type field defects were present in three others, and a ring scotoma was noted in one case. Ophthalmoscopic examination revealed definite chorioretinitis morphologically consistent with a luetic basis in eight of the 20 patients, or 40% of the series. Other fundus findings were noted, and in nine cases the fundus examination was within normal limits. Some degree of deafness apparent at a conversational level was found in four cases, or 20% of this series.

Stigmata of congenital syphilis were evident on inspection in eight patients, or 40% of the series. Frontal bossing, saddle nose, rhagades scars, mulberry molars, marked dental caries, high-arched palate, and short little fingers were assessed in these patients. One can palpate a notched scapula through the patient's clothing, and this finding was helpful at times.

The optic nerve was not remarkable on ophthalmoscopic examination in 18 patients. One case did present with active optic neuritis as evidenced by small hemorrhages on the disk margins, however. Focal segmental pallor was found in some patients, but was a minimal finding that required careful scrutiny.

The serologic findings were of particular interest in this study. A serum VDRL test was obtained in 19 cases. This was nonreactive in 14 patients (73%), weakly reactive in two (11%), and reactive in three cases (16%). A serum FTA-ABS test was obtained in 17 cases. This was nonreactive in five patients (29%), borderline in four cases (24%), reactive in six cases (35%), and was conflicting (reactive on one occasion, nonreactive on another) in two cases (12%). A TPI test was obtained in only three patients. One of these was of interest in that the TPI test was reactive, but the FTA-ABS test was nonreactive. In another patient, the TPI was nonreactive, but the FTA-ABS test was borderline. In the third patient, the TPI test was nonreactive, but an FTA-ABS test was not recorded.

The aqueous humor was studied by dark field examination in 10 patients. This was definitely positive for motile treponemes in one case, suspicious in one other case, and negative in eight patients. The cerebrospinal fluid was studied in six patients. Dark field examination was strikingly positive in one of these cases, with seven treponemes seen in one microscopic field. The cerebrospinal fluid was borderline to slightly elevated in two patients (45 and 60 mg%). Three of the fluids were completely negative.

## Discussion

Since the time of Jonathan Hutchinson (1858-63), it has been known that over 90% of cases of diffuse interstitial keratitis occur in syphilitic patients. Interstitial keratitis is due to acquired syphilis in 4% of cases, and the other 6% of cases have been due to tuberculosis, sarcoid, trypanosomiasis, onchocerciasis and other rare infections. Therefore, a careful slit-lamp examination of a patient with typical interstitial keratitis, showing a deep silvery-sheen like opacity in the posterior corneal stroma, accompanied by the presence of ghost vessels, enables one to make a clinical diagnosis of prior syphilitic infection with greater than 90% accuracy. This is thus an important clinical prototype by which to evaluate laboratory tests. Syphilitic interstitial keratitis has been presumed to be an allergic reaction to the treponeme for the following reasons: (1) in the newborn or stillborn infant Treponema pallidum organisms often abound and yet the cornea is clear and the eye white and quiet; (2) in the eye with active or late interstitial keratitis, however, treponemes are found in the cornea only in small numbers and after careful search; (3) there is a characteristic delay between onset of infection until appearance of the clinical process, with 50% of cases recognized between five and 15 years of age, and 85% of the cases found by the age of 25 years; (4) the process does not respond to penicillin or heavy metal therapy; and (5) the process often shows prompt clinical improvement on topical corticosteroid therapy.

Spicer's[4] classic series of 700 cases of interstitial keratitis revealed a sex incidence of 38% males and 61% females in congenital syphilis. He found that the process was bilateral in congenital cases, with the second eye involved within 12 months in 75%. All cases in this report were bilateral. In 9% of cases there are recurrences, and these may be as late as 15-30 years after the primary attack. The occurrence of glaucoma years after interstitial keratitis, which may first appear in early adult life, has been known since the time of Hutchinson. In the natural course of the disease 70% retain 20/20 to 20/60 vision with no therapy, and only 10% have vision less than 20/200.

Today, most cases of interstitial keratitis are adult patients seen in eye clinics, diagnosed by careful biomicroscopic examinations. The acute attack, so prevalent in Spicer's day, is seldom noted. However, the clinician should be aware of the significance of the slit-lamp detection of interstitial keratitis. Emphasis is placed here upon clinical diagnosis. The disease is seen in females in a ratio of 3:1, often at about 40-50 years of age, and 75% give a history of significant ocular inflammation in childhood. A careful family history for reactive serologic tests, fetal wastage, Cassewitz law, previous treatment, and other manifestations of syphilis will be positive in 75% of the cases. The pupils are typically spared, and do not commonly show light-near dissociation which is so prevalent in late-acquired syphilis. Glaucoma is present in 25% of cases. Careful search for stigmata of frontal bossing, depressed nasal bridge, Hutchinson's teeth, marked dental caries, hearing loss, sparse outer brows, high-arched palate, and short little fingers will often be rewarding. Perivascular pigmentation, sheathing of vessels, and salt-and-pepper chorioretinitis changes are seen on ophthalmoscopy in at least 40% of these patients.

This study emphasizes, however, the frequency of seronegativity in patients with interstitial keratitis. The routine reagin (VDRL) test was definitely reactive in only 16% of cases. If weakly reactive tests are included—and it should be remembered that weakly reactive reagin tests may be reported as nonreactive or weakly reactive on repeat testing in 50% of laboratories—some reagin reactivity was found in 27% of cases. However, 75% of patients with typical syphilitic interstitial keratitis will be nonreactive on serum VDRL testing.

Furthermore, even specific (treponemal) tests are often nonreactive in interstitial keratitis. The serum FTA-ABS test was definitely reactive in only 35% of cases in this

series. If one includes borderline tests and conflicting data, some FTA-ABS reactivity was noted in 71% of the cases. However, 29% of the cases showed nonreactive serum FTA-ABS tests. It is important for the ophthalmologist to be aware of the frequency of complete seronegativity in patients with late congenital syphilitic interstitial keratitis.

If the patients have not been previously treated for syphilis, one of two courses of therapy has been advised: Erythromycin 250 mg four times daily and probenecid (Benemid) 500 mg orally twice daily for 30 days has recently been proposed. Ampicillin 1g and oral probenecid 0.5 g three times daily for 30 days may also be given. The patient should be seen one month after treatment and the decision should then be made as to whether or not therapy should be continued. If the patient is worse, therapy should be discontinued. If the patient is the same, clinical discretion is in order. If the patient is better, the therapy should be continued until maximum improvement is obtained. This may often require a total course of three months. A trial with high myopic cylindric corrections is in order in these patients. It is suggested that the ophthalmologist put a −9.00 sphere with a +5.00 cylinder in the trial frame and allow the patient to turn the cylinder axis at will. This will on occasion produce surprising improvement in patients with a difficult retinoscopy, and who are unable to use a pin-hole aperture well. Some patients develop secondary band keratopathy superimposed on interstitial keratitis, and one man was treated with EDTA therapy with improvement from 20/200 to 20/25 corrected vision. Medical therapy for one month before and until one month after intraocular surgery appears in order in these patients because of recent evidence of the persistence of treponemes in such cases. One patient in this series was so treated and had a penetrating keratoplasty and later a lens extraction with improvement of vision from 5/200 to 20/20 in the involved eye. In a study[5] of aqueous humor and cerebrospinal fluid made in a series of patients with late treponemal disease, treponemes were found in 26 of 101 cases studied with the fluorescent antibody stain.

In summary, although serum VDRL and FTA-ABS tests should definitely be obtained on patients with late interstitial keratitis, it should be stressed that this disease requires a clinical diagnosis. An adult woman with a history of ocular inflammation in childhood, sparse outer brows, Hutchinsonian teeth or full dentures, prominent frontal regions, moderate hearing loss, whose mother lost two pregnancies during the late first or early second trimester or who had a stillborn fetus before the birth of the patient, and who shows typical biomicroscopic signs of interstitial keratitis, should be diagnosed as congenital syphilis on clinical criteria with no reservation. In late interstitial keratitis deriving from congenital syphilis, seronegativity is a common finding.

## Summary

A review of 20 cases of late syphilitic interstitial keratitis revealed the frequent finding of seronegativity in such patients. The VDRL test was nonreactive in 74%, weakly reactive in 11%, and reactive in 16% of these cases. The serum FTA-ABS test was nonreactive in 29%, borderline in 24%, reactive in 35%, and conflicting in 12% of the cases. Emphasis is placed upon clinical criteria for diagnosis.

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# LONG-TERM TOPICAL POLY I:C IN EXPERIMENTAL CHRONIC OCULAR HERPES SIMPLEX INFECTION

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Topical synthetic double-stranded polyinosinic polycytidylic acid (Poly I:C) is moderately active against acute experimental herpes simplex (HS) keratitis in rabbits,[1,2] although its antiviral effect is not nearly as potent as that of idoxuridine.[3,4] If the same Poly I:C treatment regimen was continued beyond the period of acute infection, few recurrences were noted initially; however, after six to eight weeks recurrent keratitis, as measured clinically, occurred with equal frequency in treated and control groups.[3]

The present study was undertaken to investigate the effect of Poly I:C on a different facet of the problem. We attempted to discover whether long-term, low-dosage topical Poly I:C therapy could suppress or eradicate the disease in established chronic ocular HS infection. A previously described rabbit model[5] which mimics human recurrent ocular HS infection was employed. In contrast to other studies basing recurrence rate on clinical observation, this investigation was conducted using the virus culture method. Recovery of the agent from the tear film has been shown to be a more sensitive indicator of recurrent virus release.[5,6]

## MATERIAL AND METHODS

*Infection*—The unscarified eyes of male New Zealand albino rabbits weighing approximately 2 kg were infected by instilling two drops of high-titer herpes simplex virus (HSV) into the conjunctival cul-de-sac. The eyelids were closed and gently massaged against the globe for 10 seconds. The infecting suspension was from the 12th passage of McKrae strain HSV in primary rabbit kidney cell cultures and in this tissue had $ID_{50}$ of $10^{7.3}$ per 0.1 ml.

During the three-week period of acute infection daily slit-lamp biomicroscopic evaluation of the eyes, using 0.25% fluorescein, was carried out. Based upon these observations, rabbits were divided into groups containing equal numbers of mildly, moderately, and severely affected animals. These groups were then randomly assigned to receive drug or placebo therapy.

*Experimental design*—Beginning 30 days after virus inoculation, when clinical evidence of acute infection had subsided, culturing and treatment of eyes was initiated. Each morning (six days a week) conjunctival swab cultures were taken. Immediately afterwards, both eyes of each animal received either two drops of Poly I:C (1 mg/ml) or placebo, as outlined below.

Cross-over design was selected for these experiments, since it is both an efficient way to demonstrate drug effect and an acceptable means to obtain information about the effect of therapy after treatment is stopped. Experiment 1 was a non-blind complete cross-over study. All animals treated with Poly I:C in the first half of the experiment were treated with placebo in the second half and vice versa (Table 1).

Experiment 2 was carried out in a blind fashion and was of the half-group cross-over type. After 15 weeks of therapy, all treatment was discontinued for three weeks. When therapy was reinstated, half of the placebo group then received Poly I:C and half continued to receive placebo medication. Half of the previously Poly I:C treated group continued to receive Poly I:C while the other half of that group then received placebo therapy (Table 2).

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TABLE 1

EXPERIMENT 1—NON-BLIND COMPLETE CROSS-OVER DESIGN

| | First Treatment (12 Weeks) | Second Treatment (17 Weeks) |
|---|---|---|
| Group 1 | Poly I:C | Placebo |
| Group 2 | Placebo | Poly I:C |

*Poly I:C*—Poly I:C was obtained from two commercial sources (Biopolymers Laboratory and PL Biochemical Company). With minor variations, each lot of double-stranded polymer was handled and stored according to the manufacturer's recommendation. In the second half of Experiment 2, the Poly I:C (PL Biochemical Company) was reconstituted in phosphate-buffered saline at pH 7.6 rather than at pH 6.8. At the conclusion of the study, an aliquot of each batch of Poly I:C used was tested by us and by Dr. Samuel Baron for in vitro interferon-inducing activity, employing methods outlined elsewhere.[7] Except for the instance cited below, the activity of the Poly I:C employed in this study was equal to and usually greater than NIAID Poly I:C standard.

*Virus cultures*—Conjunctival swab cultures were taken as previously described.[8] Swabs were immediately inoculated onto primary rabbit kidney cell monolayers grown in two-dram rectangular perfume bottles containing 1 ml of medium (Eagle's minimal essential medium supplemented with 10% fetal calf serum, 10% NCTC 135, glutamine, penicillin, streptomycin, and amphotericin B). Cultures were incubated at 35°C in 5% $CO_2$ atmosphere and read daily. After 10 days all normal appearing cultures were recorded as negative and discarded. All positive, suspicious, and degenerating cultures were frozen at −70°C for passage. Only those cultures showing typical HS cytopathic changes in the second passage were accepted as positive HSV isolations. To verify the reliability of cytopathic diagnosis, 50 randomly selected, second passage positives were subjected to standard microneutralization testing. All were definitely identified as HSV.

*Statistical analysis*—On the assumption that the drug had no effect on recurrence rate (null hypothesis), the number of HSV isolations should be approximately equal between groups (i.e., a "50-50 split" would be expected). The probability (p) of the observed splits (weighted when necessary for comparison) was obtained from a binomial probability table.

## RESULTS

In chronically infected rabbit eyes, Poly I:C, as administered, suppressed the number of HSV isolates obtained during the first 10 to 12 weeks of treatment. After this period of time, the number of positive cultures was approximately equal to that of placebo-treated controls despite continued therapy. Except as otherwise indicated, results reported in Tables 3 through 6 are those obtained during the consecutive weeks in which Poly I:C was considered effective.

*Experiment* 1—The results of this experiment are shown in Table 3. In Part 1 of this experiment there were 40 positive cultures in 14 placebo treated eyes for an average of 2.9 positive cultures per eye. In the same 10-week period the Poly I:C treated group yielded two HSV isolates from eight eyes, an average of 0.25 positives per eye. During the last two weeks of Part 1, Poly I:C appeared to lose its effectiveness (the number of positive cultures was similar in the

TABLE 2

EXPERIMENT 2—BLIND HALF-GROUP CROSS-OVER DESIGN

| | First Treatment Period (15 Weeks) | No Treatment Period (3 Weeks) | Second Treatment Period (18 Weeks) |
|---|---|---|---|
| Group A | Placebo | | Poly I:C |
| Group B | Placebo | | Placebo |
| Group C | Poly I:C | | Placebo |
| Group D | Poly I:C | | Poly I:C |

two groups, Poly I:C = 13, placebo = 16).

Therapy was switched in the second section of the experiment. The eyes in which Poly I:C was discontinued did not yield more positive cultures (20 isolates from eight eyes) than would be expected for placebo treated eyes (i.e., there was no rebound phenomenon). However, the previously placebo-treated eyes which had a large number of HSV isolates (40) in Part 1 now showed only six positive cultures in 12 weeks of testing. Again, the effectiveness of Poly I:C appeared to be limited, lasting 12 weeks in this trial despite continued therapy. For the last five weeks of the experiment, the number of positives in both groups (result not shown in Table) was the same (placebo = 6, Poly I:C = 7). The difference in the number of positive cultures obtained from Poly I:C-treated animals and the controls during the consecutive weeks in which the drug appeared to be effective was highly statistically significant ($p = < 0.00001$).

*Experiment* 2—This was performed on a blind basis and confirmed the previous findings. Tables 4 and 5 show data accumulated during the period in which Poly I:C was effective. Not included are the results from eight weeks of therapy inadvertently carried out with an inactive batch of Poly I:C (16 positive cultures in control eyes and 14 in Poly I:C treated eyes). During the seven weeks when active Poly I:C was employed, there were nine HSV isolates in 14 Poly I:C-treated eyes and 36 isolates in 16 placebo-treated eyes. When therapy was stopped for three weeks, the number of HSV isolates was essentially the same in all groups (Group A = 10, Group B = 11, Group C = 14, Group D = eight). In the last section of Experiment 2, half of each treatment group was switched to the opposite therapy. During the 12 weeks in which Poly I:C was effective, there were five positive cultures in 16 eyes as compared with 40 positive cultures in 14 eyes of placebo-treated animals.

Further analysis of this half-group crossover experiment yields some very interesting information (Table 5). Group A (placebo–Poly I:C) showed a marked decrease in the number of positive cultures when placed on Poly I:C. Group B (placebo–placebo) yielded about the same number of isolates in both parts of the trial. Group C (Poly I:C–placebo) showed few positive cultures while on Poly I:C and a normal number when changed to placebo therapy.

TABLE 3

RESULTS OF EXPERIMENT 1

| | Placebo | Poly I:C | Probability |
|---|---|---|---|
| Part 1 (10 weeks*) | | | |
| No. positive cultures | 40 | 2 | 0.00001 |
| No. of eyes | 14 | 8 | |
| Part 2 (12 weeks*) | | | |
| No. positive cultures | 20 | 6 | 0.00003 |
| No. of eyes | 8 | 14 | |
| Both parts (22 weeks*) | | | |
| No. positive cultures | 60 | 8 | <0.00001 |
| No. of eyes | 22 | 22 | |

* Consecutive weeks during which treatment was considered effective.

TABLE 4

RESULTS OF EXPERIMENT 2 BY TREATMENT

| | Placebo | Poly I:C | Probability |
|---|---|---|---|
| First treatment (7 weeks*)† | | | |
| No positive cultures | 36 | 9 | <0.001 |
| No treatment (3 weeks) | | | |
| No. positive cultures | 21 | 22 | >0.5 |
| Second treatment (12 weeks*)‡ | | | |
| No. positive cultures | 40 | 5 | 0.00001 |
| Both treatment periods (19 weeks*) | 76 | 14 | <0.00001 |

* Consecutive weeks during which treatment was considered effective.

† In first treatment period groups A and B (16 eyes) received placebo and groups C and D (14 eyes) received Poly I:C.

‡ In second treatment period groups B and C (14 eyes) received placebo and groups A and D (16 eyes) received Poly I:C.

TABLE 5

RESULTS OF EXPERIMENT 2 BY GROUP

| | No. Positive Cultures First Treatment Period | No. Treatment Period | No. Positive Cultures Second Treatment Period | Probability |
|---|---|---|---|---|
| Group A (Placebo—Poly I:C) | 21 | | 5 | 0.001 |
| Group B (Placebo—Placebo) | 15 | | 18 | >0.3 |
| Group C (Poly I:C—Placebo) | 5 | | 22 | 0.001 |
| Group D (Poly I:C—Poly I:C) | 4 | | 0 | <0.05 |

As in Experiment 1, no rebound phenomenon was encountered. Group D eyes (Poly I:C–Poly I:C) yielded few positives in either test period, demonstrating that Poly I:C had re-established its effectiveness after a three-week lapse in treatment.

Table 6 shows the combined results of both experiments. During the 41 weeks in which Poly I:C was considered to be effective, placebo-treated eyes yielded 136 positive cultures for an average of 2.6 positive cultures per eye, while the Poly I:C-treated eyes showed 22 positives for an average of 0.42 per eye. The difference in the number of HSV isolations between Poly I:C and placebo-treated eyes in all individual trials, and for the study as a whole, was highly statistically significant. During the 20 weeks in which Poly I:C was not effective, there were 68 HSV isolates from placebo-treated eyes and 71 isolates from Poly I:C-treated eyes.

*Distribution of HSV isolations*—One extraordinary finding of these experiments is that every eye yielded at least one HSV isolation, indicating that all eyes were chronically infected. This may be a chance happening or may be in part related to the improved culture techniques discussed below.

There was a total of 360 HSV isolations from the 11,880 cultures taken during the study, an incidence of 3%. On the basis of number of isolations, some eyes would be considered high responders and others low responders. The distribution of high and low responders was evenly spread among the experimental groups and therefore introduced no bias to the results reported. The highest number of positive cultures for any eye was 22 and the lowest was one. Of eyes yielding more than one positive culture, 90% did so in more than one episode. The average number of separate episodes of virus shedding was three, and these were usually separated by a considerable time span.

## DISCUSSION

In human ocular herpes simplex infections, fairly adequate methods exist to treat acute epithelial disease. Vision is usually compromised by repeated bouts of the disease with accompanying stromal or endothelial damage and iritis. While better agents to treat epithelial herpes would be desirable, therapeutic means to protect against initial ocular infection, to prevent deep herpetic disease, or to eliminate recurrent infection are needed. It is with the latter goal in mind

TABLE 6

SUMMARY OF RESULTS OF EXPERIMENTS 1 AND 2

| | Placebo | Poly I:C | Probability |
|---|---|---|---|
| Experiments 1 and 2* | | | |
| No. positive cultures | 136 | 22 | 0.00001 |

* During consecutive weeks in which Poly I:C was effective.

that this study of experimental treatment of chronic HSV infection in rabbits was undertaken.

Unfortunately, chronic ocular HSV infection in rabbits was not eradicated by long-term, low-dosage Poly I:C therapy. When therapy was stopped or became ineffective, the number of positive cultures from treated eyes was the same as that from controls. However, during the first 10 to 12 weeks of treatment, Poly I:C significantly decreased the number of HSV isolations obtained from chronically infected eyes. With cessation of therapy for three weeks, another 10- to 12-week period of responsiveness to Poly I:C was established. The mode of Poly I:C action is assumed to be the induction of local interferon production,[2,4] but no direct evidence for this hypothesis was obtained or sought in these studies. The regimen in which the Poly I:C is given is of importance. In a pilot experiment we found that Poly I:C given topically three times a day every three days had no effect on the number of HSV isolations obtained from chronically infected rabbits.

In spite of the fact that man is less responsive to the interferon-inducing activity of Poly I:C than rabbits,[4] the polymer might be useful in temporarily suppressing herpes recurrences in man. Such a study is presently underway elsewhere.

The true incidence of chronic ocular HSV infection in man or experimentally infected animals is difficult to determine. However, the fact that all 52 eyes in this experiment shed virus long after the acute infection indicates that the incidence in rabbits may be much higher than suspected previously.[5,6]

Analysis of many experiments using this model has allowed us to make three rather general observations: (1) As previously reported, there appears to be a clustering of HSV isolations in any group of animals.[5] This clustering is in periods lasting 30 to 40 days occurring every 60 to 120 days. (2) The severity of the initial infection is in no way related to the number of HSV recurrences. (3) There appear to be fewer positive cultures obtained as the time from acute infection increases. The reasons for the above phenomena are at present obscure.

Obtaining a higher than usual isolation rate is at least in part due to improved culturing techniques. Freshly obtained culture material was inoculated directly onto a very sensitive herpes virus indicator, primary rabbit kidney cell cultures. With present procedures, this tissue can be maintained for the full period of observation with few instances of contamination or degeneration. Only 318 cultures were contaminated with fungus or bacteria and had to be eliminated, a rate of less than 3%. Important also was the practice of retesting all suspicious or degenerating cultures. Of 446 such repassed specimens, which would have been discarded in our previous studies, 31 or approximately 7% proved to be harboring HSV.

In spite of an improved yield of positive cultures and improved experimental design, the rabbit recurrence model remains a difficult research tool, requiring extended periods of culturing to obtain statistically significant results. However, until a better test system is developed we will continue to use this model to investigate the effect of therapeutic agents on recurrent ocular herpes simplex infections.

## Summary

Daily topical Poly I:C therapy was tested for its effect upon chronic recurrent ocular herpes simplex infection in rabbits. Fifty-two chronically infected eyes were cultured six days a week for seven to nine months. Topical Poly I:C repeatedly produced a marked, but temporary supression of positive herpes cultures—placebo-treated eyes yielded six times as many isolations (136) as the drug-treated eyes (22) during the first 10 to 12 weeks of therapy. After that period, continued therapy had no effect. However, if Poly I:C were witheld for three weeks, responsiveness to the drug was again established. No rebound in the number of virus

isolations was found when treatment was discontinued or became ineffective. The highest incidence of chronic herpes infection ever reported was encountered in these experiments. All 52 eyes (or 100%) shed culturable herpes virus.

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## Ophthalmic miniature

As he sat on the grass and looked across the river, a dark hole in the bank opposite, just above the water's edge, caught his eye, and dreamily he fell to considering what a nice snug dwelling place it would make for an animal with few wants and fond of a bijou riverside residence above flood level and remote from noise and dust. As he gazed, something bright and small seemed to twinkle down in the heart of it, vanished, then twinkled once more like a tiny star. But it could hardly be a star in such an unlikely situation, and it was too glittering and small for a glow-worm. Then, as he looked, it winked at him, and so declared itself to be an eye; and a small face began gradually to grow up around it, like a frame 'round a picture.

Kenneth Grahame
*The Wind in the Willows,* 1908

# NOTES, CASES, INSTRUMENTS

## HETEROCHROMIA ASSOCIATED WITH COLOBOMA OF THE IRIS

ROBERT C. DREWS, M.D.
*Clayton, Missouri*

AND

GUILLERMO PICÓ, M.D.
*Santurce, Puerto Rico*

Each of us has seen a patient who had both heterochromia and a coloboma of the iris. We could find no prior description of this association.

### CASE REPORTS

*Case* 1—A six-year-old white girl was seen in November, 1966, at the University of Puerto Rico because of a defective left eye, present since birth. Her medical history was non-contributory. There were no other physical abnormalities.

The right iris was thinner at the six o'clock position than elsewhere. There was a complete coloboma of the left iris at the six o'clock position. The right iris was blue and the left was brown. The left cornea was smaller than the right, but the eye was not microphthalmic. Left esotropia measured 55 prism diopters for distance and near. A small coloboma was present inferiorly in the right choroid. A large coloboma of the left choroid extended from a point near the disk to involve a large area inferiorly. The optic disks were normal. Visual acuity was 20/25 in the right eye and light perception and projection in the left. Retinoscopy following atropine instillation indicated a correction of +2.50 sph ⊃ −0.75D cyl.ax.180° for the right eye. It was impossible to perform accurate retinoscopy on the left eye.

When this child was last seen in May, 1970, the findings were unchanged.

*Case* 2—A 57-year-old woman was first seen in May, 1955, for a mild conjunctivitis in both eyes. A coloboma had been present in the left iris since birth. Vision in this eye, always slightly less than in the right, had previously been corrected to 20/38. Corrected vision in the right eye was 20/15.

The right iris was blue and the left a yellowish blue. There was no microphthalmos. Early arteriolarsclerosis was present. There was no sign of a choroidal coloboma in either eye, but a partial coloboma was present in the left iris. The right eye showed no evidence of prior iritis. Astigmatism in the left eye measured 3.50 diopters. Visual acuity with best correction was 20/25 in the right eye and 20/60 in the left.

This patient has been followed at irregular intervals. In 1963, Goldmann perimetry showed normal visual fields. In 1968, a cortical cataract in the left eye was more advanced then one in the right eye.

In a rabbit colony bred by Jesberg[1] for coloboma of the uvea, a few of the animals were born with heterochromia rather than a coloboma. Following this experience, Jesberg saw a patient with both coloboma of the iris and heterochromia. In Jesberg's patient, the eye without the coloboma had hyperpigmentation of the conjunctiva as well as the iris. We submit that Jesberg's experience, together with the patients reported herein, tends to suggest the association of heterochromia and coloboma as a true syndrome.

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### SUMMARY

Coloboma of the iris was associated with heterochromia in two female patients. In both, the darker and amblyopic eye had the coloboma. Another investigator has described a similar patient, and in this case, too, the eye without a coloboma had hyperpigmentation. In a colony of rabbits bred for coloboma of the uvea, a few were born without coloboma, but with heterochromia instead.

### REFERENCE

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## NEW SURGICAL INSTRUMENT CARRYING CASE

DAVID J. MCINTYRE, M.D.
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Although this is an age of rapid advancement in instrumentation, we have seen little innovation in the area of surgical instrument storage and carrying. Existing cases are rather archaic combinations of little elastic straps, cardboard and loose boxes. The pri-

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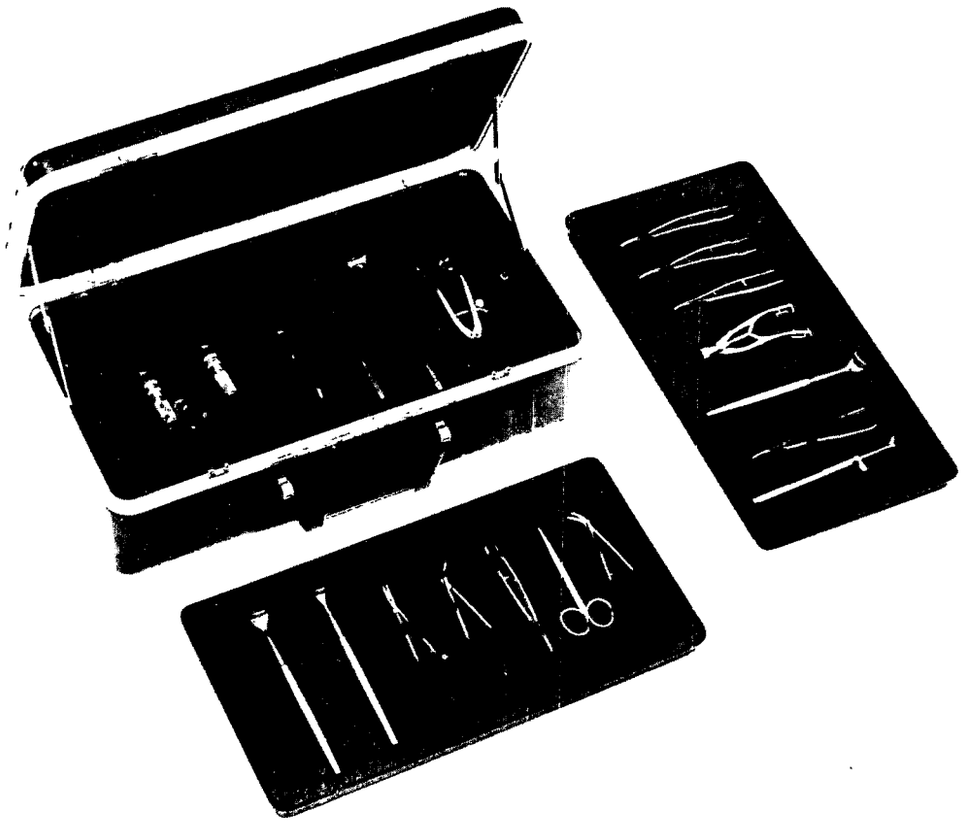


Fig. 1 (McIntyre). New surgical instrument carrying and storage case.

mary function of a case, of course, is to provide reliable protection for the vast assortment of small instruments the ophthalmic surgeon is prone to carry. Additional desirable features would be convenience, durability, compact size, and attractive appearance.

A case has been developed to meet these criteria, utilizing a new packaging concept.* Very simply stated, this case is full at all times. There is no room for instruments to move around. The case is filled with several layers of compressible plastic foam. These foam layers are molded into trays with a sufficiently rigid frame to facilitate handling. The instruments lying between the layers are held firmly in position by the compressed foam; in the absence of any instrument, foam fills the potential space. The lowest tray is equipped with a handle at each end allowing the stacked trays to be removed from, and returned to the case as a unit. When the trays are unstacked on a flat surface, each instrument is clearly visible for selection.

Immediately beneath the stacked trays, the case contains a thick foam pad which has been die-cut to hold bulky, less delicate instruments such as speculae, irrigator bulbs, cautery, and knives in their original boxes. The cores of these cutouts are held in place with narrow webs which can be easily divided for removal, but for those who must "do their own thing," an alternate pad can be cut to any desired pattern with only a sharp

* This instrument case is available from Surgical Products Division, Alcon Laboratories, Inc., Fort Worth, Texas 76101.

knife and the patience of an ophthalmic surgeon.

SUMMARY

A new surgical instrument carrying-storage case is designed on the basis of a new packaging concept. The case provides excellent instrument protection, combined with minimum weight and bulk, convenience, and durability.

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OPHTHALMIC MINIATURE

North, South; Doctor, Patient—The Anglo-Saxon doctor, when dealing with a medical problem, may handle the physical aspects of the case with commendable dexterity, but in dealing with those aspects which are not encompassed by his clinical experience, notably the patient's histrionic manner, his distrust of the doctor's opinion, and his inadequate command of English, the doctor is likely to fall back on non-medical premises, usually culturally determined, but arising from a culture which differs from the Italian one. He may regard histrionic behavior as cowardly and asking for other opinions as ungrateful or as a challenge to his concept of himself as an authoritarian figure; his inclination is frequently to reject the patient, having excluded serious physical disease, to make a diagnosis of character defect, the implication often being that the patient—and sometimes, implicitly, the race—is inferior.

In contrast, a prevailing idea in Italian communities is that the sick person is the center of attention; he considers that it is his right that others forgo their normal activities in order to tend to his needs. The "stiff upper lip" of the British society does not exist. The patient expects this attention from his doctor and believes that he has a right to inconvenience the doctor. The Italian patient thinks that he knows his disease and has his own preconceived ideas about the etiology, prognosis, and implications. Above all, he lives to discuss his illness with the doctor, and puts himself on an equal plane when doing this. To the doctor unaware of these factors, the Italian patient appears to lack confidence and, worse, he is prepared to argue and put forward concepts of disease which have a totally different basis from the doctor's. It is evident that in this situation little mutual understanding can occur, unless the underlying premises are appreciated and allowed for by the doctor and, when relevent, the underlying concepts discussed.

Anthony J. Portelli and Ivor Jones
Mediterranean gut ache
*Med. J. Australia,* 2:717, 1969

# MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

## FIFTH ANNUAL MEETING OF THE HORACIO FERRER EYE INSTITUTE INTERNATIONAL SYMPOSIUM ON OCULAR MOTILITY

Over 200 ophthalmologists from 15 countries met in Miami at the end of January, 1971, to discuss problems in strabismus at the fifth annual symposium on ocular motility sponsored by the Horatio Ferrer Eye Institute. The two and one-half day meeting was so well organized by Symposium Director Olga Ferrer, and by Program Chairman William Rubin, that it is possible only to mention the multiple nonscientific attractions of friendly cocktail gatherings, a banquet with a fabulous show, a barbecue outing with exiled Cuban guitarists. The Fontainbleau Hotel in Miami Beach housed the symposium. Arthur Linksz, the guest of honor, provided the opening paper on physiologic and anatomical factors pertinent to an understanding of squint, but in a characteristically erudite and yet modest way he also provided philosophical insight into the problems of absolute and subjective localization, amblyopia, and the crowding phenomenon. He provided an appreciation of the knowledge which accumulated many years before the advent of so-called pleoptic methods.

Hermann Burian, honorary president, dealt with the role of the AC/A ratio in the production of the two main forms of accommodative esotropia, and Harold Brown emphasized that a high AC/A ratio may be associated with an exodeviation almost as frequently as with an esodeviation. John Hermann discussed the rate of the movement of the convergence which occurs in response to an accommodative stimulus (the so-called "pace response") which can be measured by electro-oculography and which leads to a better understanding of the implications of the AC/A ratio in the management of an accommodative squint. Rethy considered that the term "partially accommodative," as applied to an esotropia, is usually a misnomer because it applies to a squint in which there is a failure to unmask the full extent of the underlying accommodative factor. Charles Windsor said that he thought that the gradient method is more reliable than the heterophoria method in determining the AC/A ratio because it introduces other factors such as the influence of proximal convergence. He pointed out, however, that the gradient method may be uncertain in the young child because its accuracy depends on an exact degree of accommodative change in response to different spherical lenses.

The nature of the A and V phenomena was discussed by Leonard Apt, Webb Chamberlain, Joseph Goldstein, and Joseph Lang. The necessity of using a target which excites a precise degree of accommodation during the measurements of the deviation in the different positions of gaze was stressed, and evidence was produced which casts doubt on the importance of anomalies of the horizontal recti in the genesis of the phenomena.

Detailed discussons on early convergent strabismus were led by Albert Ciancia, Joseph Lang, and Robert Reinecke. Late convergent strabismus was the topic of Bruno Bagolini, Pierre Vital Berard, and Glen Gibson, and divergent strabismus was discussed by Robison Harley, Emma Limon-Brown, Donelson Manley, Suzanne Veronneau-Troutman, and Charles Windsor. These discussions occupied the main part of the first afternoon. The association of congenital and latent nystagmus was mentioned, and attention was directed to the peculiar form of estropia of late onset which occurs in myopia. The difference between the true divergence excess form and the pseudodivergence (simulated divergence) excess form of exodevia-

tion were outlined. The importance of pre- and postoperative orthoptic treatment in the mangement of exodeviations was stressed.

In a discussion of vertical muscle imbalances by Webb Chamberlain, Jorge Ferrer, Hiram Hardesty, Robison Harley, Phillip Knapp, and Keith Lyle, the condition of alternating sursumduction was described in detail and also its distinction from a simple bilateral overaction of the inferior obliques.

In the opening paper of the second day, Keith Lyle (guest of honor) provided a comprehensive survey of the various forms of ocular palsy that follow trauma, including their surgical management. This was followed by a paper on the significance of nystagmus in early childhood presented by Kenneth Wybar, with emphasis on the importance of distinguishing between idiopathic congenital nystagmus, which is probably the result of a minor derangement of the centers in the brain stem, and the pendular type, which is probably the result of some syndrome or an ocular albinism which is only detected in the early stages by refined methods of investigation.

A discussion on various forms of supra and infranuclear paralytic strabismus was presented by Robert Jampel, Keith Lyle, Robert Reinecke, and Kenneth Wybar. They produced some interesting clinical and experimental observations which suggest that the condition of aberrant regeneration of the oculomotor nerve (the misdirection syndrome) is the result of a mass response of some or all of the nerve fibers in the distal part of the nerve, rather than the result of a misdirection of axons which pass into the distal part of the nerve from the proximal part. The finding of a co-contraction of the superior rectus and inferior rectus is part of the evidence for this concept. Discussion also centered on a peculiar form of dissociated vertical movement which may be the result of a "cross-wiring" of the supranuclear pathways of the centers of the brain stem.

The lesions of the orbit which lead to anomalies of ocular movement were dealt with by G. M. Bleeker, John Dyer, and Byron Smith. There is geometric evidence that the enophthalmos which occurs in a blow-out fracture accentuates the hypotropia and limitation of elevation of the affected eye.

The afternoon session of the second day opened with a discussion on contact lenses in sensory and motor anomalies presented by John Dyer, Olga Ferrer, Louis Girard, and John Hermann. The influence of contact lenses on the AC/A ratio was discussed; in myopia the AC/A ratio is higher with contact lenses than with spectacle lenses, so that contact lenses are less helpful in the management of an esodeviation than in an exodeviation. In hypermetropia it is lower with contact lenses than with spectacle lenses so that contact lenses are more helpful. The importance of contact lenses in the postoperative management of congenital cataracts was stressed, but a subsequent discussion emphasized the special problem of rubella cataracts because of the endophthalmitis which is prone to follow even faultless surgical technique. The occurrence of a stimulus deprivation amblyopia is also a possibility in any form of congenital cataract which is not susceptible to postoperative treatment with contact lenses. The use of soft contact lenses in aphakic children was evaluated by John Dyer. This panel was followed by another one on ocular muscle surgery. The tendon lengthening procedures of partial tenotomy and partial myotomy was discussed by Harold Brown, and the surgical treatment of congenital nystagmus was discussed by Keith Lyle and Leonard Apt, who provided interesting comments on the merits and demerit of plain catgut, chromic catgut, and collagen sutures in the surgery of the extrinsic muscles.

The concluding sessions were devoted to the sensory anomalies of squint, with discussions on amblyopia presented by Eugene Folk, John Flynn, Keith Lyle, and William Rubin. The therapeutic uses of prisms was discussed by Bruno Bagolini, Pierre Vital Berard, Hiram Hardesty, Arthur Linksz,

and William Rubin, and the role of orthoptics by John Dyer, Louis Girard, Emma Limon-Brown, and Suzanne Veronneau-Troutman. These disscusants gave particular attention to the application of prism therapy in esotropia with anomalous retinal correspondence, and also dealt with the different aspects of occlusion in the management of squint. An interesting contribution by John Flynn showed that Mach's bands, which are revealed by viewing a luminance gradient, are increased in width in the amblyopic eye. This is further indication of the complex changes in visual function which occur in amblyopia.

The meeting concluded with a discussion on the many different charts which are available for the recording of visual acuity. That there is a need to achieve a standardization of the composition and spacing of the letters in order to be able to obtain recordings which are readily comparable was pointed out by Jane Romanio and Marion Sterner.

Kenneth C. Wybar

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## SOCIETY OF EYE SURGEONS MEETING

As its parent organization, the International Eye Foundation, celebrated the 10th anniversary of its founding, the first congress of the Society of Eye Surgeons (SES) was held in Washington, D.C., on May 27 and 28, 1971. There were 233 members in attendance among a total group of 320, including guests and residents. In all, 14 foreign countries were represented. The response of the membership exceeded all expectations and emphasized the need for and the value of a congregation of ophthalmologists interested in surgery.

The opening ceremonies were impressive and included the display of our national colors by honor guards from all branches of the United States military services. John Harry King, Jr., Executive Director of the SES, and Medical Director of the International Eye Foundation, read a congratulatory letter from President Nixon, which stated in part ". . . those who have supported this great humanitarian undertaking deserve the admiration and respect of all Americans." Congratulatory cablegrams were then read from members of many countries who were unable to attend the congress.

Prof. Hans Goldman was chosen the Honorary President of this first congress and Derrick Bail presented him with a large inscribed silver tray as a memento of the occasion.

Eight of the program participants were from foreign countries, with Canada, Latin America, Europe, Asia, the Middle East, Africa and Australia particularly well represented. The papers were grouped in panels on injuries, cornea grafting, extraocular muscles, glaucoma, plastic surgery, retinal detachment, and cataract. All presentations were given in English much to the credit of our Fellows from abroad. There was no language problem so that an easy exchange of views in the discussion was possible and was most profitable. The board representation enabled us to hear details of the most current techniques in all phases of eye surgery, and we were again impressed with the unique and valuable contributions from every part of the globe. Since such studies are often slow in appearing in our literature, the Congress provided us with the opportunity to evaluate and apply the new techniques which are constantly improving operative results.

Prior to his discussion on parasitic disease of the orbit, Lorenz E. Zimmerman was made an honorary fellow of the society. R. Townley Paton, one of the guests of honor at the congress presented the distinctive plaque of membership. The highlight of the meeting was the presentation of the Vail medal to Algernon B. Reese. This gold medal honors Derrick Vail, a founding member, and to quote from Prof. Goldman's citation ". . . is an estimate of the great esteem which the society holds, not only for Dr. Vail's accomplishments in ophthalmology, but also

for his character and leadership." Dr. Reese was cited for ". . . his scientific publications, his textbooks, his versatility as a medical ophthalmologist, ocular and ophthalmic surgeon, which have given him an enviable reputation in each field." The only previous recipient of the award is Count Hernando Arruga, of Barcelona, Spain. The Vail lecture, given by Dr. Reese was entitled "Orbital surgery." It was a most complete and current review of this area of eye surgery by the surgeon who has had the greatest experience with the orbit in the United States, and perhaps the world.

The meeting was meticulously organized, but the time seemed much too short. Nearly 40 summary papers were presented by the membership on a tight schedule of just two half-days. Many excellent papers submitted could not be accepted due to the brevity of the congress.

At the Foresight luncheon for members and wives the feature was a review of the activities and accomplishments of the International Eye Foundation over the last decade. The talk, illustrated with color slides, was presented by the Foundation's Medical Director, J. Harry King, and he has kindly summarized his presentation for JOURNAL readers in an editorial in this issue.

The official reception permitted all the guests and their families to meet Prof. Goldmann and the guests of honor. Dr. and Mrs. Derrick Vail, Dr. and Mrs. Algernon Reese, and Dr. and Mrs. R. Townley Paton were in the receiving line. Ambassadors from the various countries of the members were present as were numerous other dignitaries.

To mark the Memorial Day weekend, the closing ceremonies included a most impressive event. Dr. and Mrs. Reese and Dr. and Mrs. Paton presented a wreath from the Society of Eye Surgeons at the tomb of the unknown soldiers at Arlington National Cemetery, accompanied by Honor Guards and a Marine bugler playing taps.

Each member attending the meeting received a STAR certificate (Surgical Training After Residency) established by the SES as evidence of continuing medical education.

Enthusiasm was obvious among those attending and participating. The meeting did bring out new surgical techniques—some of which were controversial, and even experimental. Many requests were made for more meetings and plans are now being formulated.

John W. McTigue

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## NEW YORK MEDICAL COLLEGE OPHTHALMOLOGY SEMINAR

The Department of Ophthalmology of the New York Medical College held its annual Seminar in Aruba, Dutch West Indies, from January 22 through January 30, 1971. The seminar theme was ocular surgery.

David Kasner presented an excellent illustrated demonstration of the surgical anatomy of the limbus. He stressed the importance of the wider upper angle and provided appropriate surgical landmarks for a variety of anterior segment procedures. Ramon Castroviejo discussed adult cataract surgery, corneal surgery, and the advantages and disadvantages of microscopic techniques. Austin Fink spoke on the suction technique of congenital pressure constant. Charles Kelman reviewed the newer methods of cataract surgery, including the use of phakoemulsification and the indication for variations in the size of the limbal incision in cataract extraction.

The session on glaucoma was opened by Ramon Castroviejo, who discussed methods of filtering surgery. Miles Galin then described techniques for surgery of congenital glaucoma including an intracameral approach in cases of totally opaque corneas. Irving Baras presented techniques of combined cataract extraction having of its high rate of success and negligible incidence of complications. Bernard Kronenberg dis-

cussed the value of cyclocryotherapy in glaucoma. He has been forced to limit this procedure to the management of desperate cases because of the low incidence of long-term value.

A corneal symposium was opened by A. Benedict Rizzuti, who discussed surgical approaches to bullous keratopathy. Dr. Castroveijo then presented his 10-year results with keratoprostheses and discussed the optics and techniques necessary to employ the newer methods for preserving and storing donor corneal material.

Ophthalmic surgical films were an integral part of the meeting and covered a wide range of subjects. The next seminar will be held in Puerto Rico at the Dorado Beach Hotel, January 14 through January 22, 1972.

Bernard Kronenberg

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## JAPANESE MEDICAL ASSOCIATION

The 18th meeting of the Japanese medical association was held April 3-7, 1971, in Tokyo. The opening ceremony was held at the Budokan on the afternoon of the third day. The main theme of the meeting was progress of medicine and ethics of physicians. There were many symposiums, special lectures, and invitational speeches. Some 20,000 physicians, technicians, and exhibitors attended this meeting with its five days of programs held simultaneously in six locations.

The 75th annual meeting of the Japanese association of ophthalmology was held on April 3-4, at the Saitama Hall near Tokyo, under the chairmanship of Shinichi Shikano (Tokyo). Some 15,000 attendants, including 13,000 ophthalmologists and 200 optometrists and exhibitors, registered for the meeting.

There was no invited foreign guest, but one paper was read by a guest speaker and a symposium was held on the second day. Seventy-two free papers were presented on the first day and the morning of the second day.

In the latter half of the morning on the second day Takashi Mizukawa (Osaka), the guest speaker selected by the Japanese Ophthalmological Society, spoke on physiology. and the tears. He dealt with the re-evaluation of Schimer's test and its comparison with Mizuoka-Kamada's modification, the inhibitory effect in man of the closing of the eye on secretion rate of tears examined by an isotope dilution technique, osmotic pressure of tears studied by the Ramsy and Brown technique and inulin space determination by $^{14}$C-inulin and intracellular electrolyte concentration.

A symposium on roadway traffic and the eye featured three speakers in the early afternoon. Akihiro Suzumura (Nagoya) opened a discussion on variation of dynamic visual perception of spatial objects. Harutake Matsuo (Tokyo) presented a paper on visual acuity of car drivers and seamen. In his survey of visual acuity of licensed car drivers, he found 49 (13%) out of 424 car drivers whose visual acuity with or without glasses was below standard, and he stated that accidents were caused by reduced visual acuity in the aged and in those with night myopia. Sodium street lamps caused drivers difficulities in discriminating colors. Iwao Iinuma (Wakayama) closed the session with his report on problems of disabling glare. He concluded that a driver whose eyes are exposed to a glare might become suddenly unable to see when the light goes out. As roadway signals, bright color lights are not always easy to discriminate, a bright red light being sometimes misperceived as yellow.

Among the 72 free papers, one of outstanding interest was presented by Ken Ohta (Sagamihara). He dealt with a peculiar, heretofore unknown eye disease seen in the Saju district in Nagano prefecture caused by organophosphorous insecticides. The patients complained of blurred vision, epiphora, headache, perspiration, polydipsia, dizziness, tremor, and diarrhea. They showed swollen disks, atrophy of the optic disk, spasm of the ciliary muscles, cataract, disturbance of eye motion, miosis or mydriasis in severe cases accompanied by narrowed

visual fields. Neurologic examinations revealed increased or reduced deep tendon reflexes, cranial nerve palsy, atrophy of the limb muscles, gait disturbance, tremor, clonus, and sensory disturbances. He also found abnormal liver function and paranitrophenol in the urine.

Kanji Okuda and associates (Okayama) illustrated ocular disorders in subacute myelo-optics neuropathy. The ocular histopathology of six autopsy cases was discussed ascribing the cause to degeneration of macular fibers of both optic nerves and degenerative disappearance of retinal ganglion cells. They also confirmed that these symptoms could be induced by chinoform administration in animals experimentally.

Hiromitsu Yamanaka (Kobe) related the mode of inheritance of Leber's disease. He examined all members of three families with this disease and was able to establish that inheritance of Leber's disease follows Lossen's law. He strongly supported the assumption, based on investigation of carrier ratio, that every daughter of a carrier inherits the trait. All males examined had a predisposition for this disease. The mode of inheritance was strongly suspected to be cytoplasmic.

Yoshiaki Taniguchi (Kagoshima) presented electron microscopic observations on small blood vessels of the iris of patients with diabetes. The basement membrane of the small vessels became extremely thickened by the increase of reticular fibers and the existence of dense debris. Many glycogen granules were observed in some endothelial cells, pericytes, and the vascular lumen.

The next meeting will be held in Okayama in 1972 under the chairmanship of Kanji Okuda. Noboru Kumitomo (Tokyo) was selected as a guest speaker by the association. A symposium is planned on the subject of infectious diseases of the eye. It will be led by Yukio Uchida (Tokyo), Shusaku Kitano (Tokyo), and Shunsaku Kobayashi (Yamaguchi).

Fumio Kandori

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## THE NEED FOR STANDARDS IN TESTS OF VISION

One means of advancing clinical science is the adoption of standard test procedures by all clinicians. This allows the exchange of patient data and comparison of findings by different investigators. For example, such standards exist in tonometry, and in quantitative perimetry. In fact, a major contribution of the Berne and Tübingen schools has been to provide us with equipment for perimetry which may be calibrated and which has controllable and definable stimuli.

In order to progress further in this sense, added standards need to be formulated. In particular, visual acuity and tangent screen field tests need to be defined more effectively.

The late Prof. Paul Fitts of the University of Michigan used to state that a threshold for a psychophysical response could be defined at four levels: detection, recognition, interpretation, and correlation. Each level requires a different degree of neural or cognitive activity. Visual acuity thresholds represent an excellent example of this four-level response scale.

1. A detection threshold (in older terms

"minimum visible") as applied in clinical practice today is really only determined in the optokinetic nystagmus test, where it is assumed that if the repetitive stripes are detected, fixation on the pattern will occur (slow phase of nystagmus).

2. A recognition threshold (minimum separable) requires the patient to report to the clinician the presence of one object or two, or the direction toward which the fingers of the illiterate "E" (or the opening of the Landolt "C") are pointing.

3. An interpretation threshold requires the evaluation or interpretation of pattern, such as the letters usually employed on a Snellen chart. For example, in the English language there is only one letter with a triangular shape, base down—the letter A. In fact, the interpretation of this letter does not even demand resolution of internal structure. Similarly, there are two letters having triangular shapes, base up—V and Y—and so forth. Thus prior knowledge of letter shapes and interpretation of form enters into such judgments.

4. Correlation thresholds involve interactions between forms. Simple examples are words. One implication is that the whole is greater than its parts; that is, even if the word "the" is somewhat blurred, we are familiar enough with the general shape or form of this word that we can detect this letter group readily, particularly when it is used in a proper sequence of words. Most "near" tests of visual acuity involve reading cards requiring this type of advanced cognitive skill.

Thus, the several tests of visual acuity commonly used require different levels of response, varying degrees of education and cognitive skill, and the integrity of different neural processes. The problem is further compounded in near visual acuity tests where there are bewildering arrays of test cards, recording schemes, and poor standardization of test lighting and measurement distances. Here is the perfect example of an area requiring the development of better standardized test procedures in order to advance fine testing of response skills and exchange of data between clinicians.

With the tangent screen, we suffer the indignity of having the wrong unit specified as our standard. The oft repeated figure of "seven foot candles falling on the tangent screen" does not take into consideration the reflectance properties of the screen and targets employed. Hence targets may be flat or spheres, and be coated with anything from matté to luminescent paints. Contrast varies because of the use of different colored backgrounds having nonuniform reflectance properties. In short, we have no standard! Luminance and contrast properties need to be properly specified. In addition, there are absolutely no accepted specifications for colored test targets, and hence this potentially valuable phase of clinical testing has not had general acceptance.

Not only do we need to have such standards formulated, but the professions must be educated toward their application.

Jay M. Enoch

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## CORRESPONDENCE

### Blow-out fractures

Editor:

American Journal of Ophthalmology:

Articles and books on orbital fractures, especially of the blowout variety, are increasing in frequency. Some emphasize better methods of radiologic diagnosis and some concentrate on clinical evaluation of the factors which indicate or contraindicate surgical exploration. All of them, however, seem to take the position that once a fracture is located, the herniated material reduced, and an alloplastic plate (Supramid Extra, Teflon, Cranioplastic, etc.) used to cover the break so that further herniation cannot occur, a satisfactory end result will automatically result. This isn't true because the vertical rectus muscles—especially the inferior rectus and sometimes the inferior oblique—are

sometimes so damaged that they cannot function properly. All too frequently patients are encountered whose downgaze fusion (which is much more important than upgaze fusion) was better before the fracture was repaired than afterwards.

For those who are carefully studying these patients, as we are, we recommend that at the initial examination careful photographic records be made of the patient's eyes in the primary position, and in upgaze and downgaze. If the horizontal motions seem abnormal, as might result from either an abducens paralysis or a blow-out fracture of the medial orbital wall, photographs with eyes right and eyes left should be added. Since the inferior nasal wall can be broken by a blow from a fist to the orbital rim, special attention should be given to testing the function of the inferior oblique, as this muscle arises from this bony area.

If there is a delay between the time of the first examination and the time of surgery, photographic records should be repeated. Then, several weeks after surgical repair, photographs from the same angles should be taken again. When possible, prism cover measurements and preoperative and postoperative forced duction tests should be made. These will give us a better basis for study and will point particularly towards problems yet unsolved, such as (1) how much damage the inferior rectus muscle has sustained if it is the presenting tissue that batters the orbital floor, and (2) when and how much should the vertical muscles be recessed or resected in trying to correct diplopia.

Richard Dortzbach offers a surgical suggestion: When the incarcerated muscles for which you have been searching comes into view, don't seize and wrench it! This could be the coup de grace for the nerve supply. Fracture the bone some more and let the muscle or its capsule energy.

Alston Callahan
*Birmingham, Alabama*

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## METASTATIC ENDOPHTHALMITIS

Editor:

American Journal of Ophthalmology:

I read with interest the article entitled Metastatic endophthalmitis associated with injection of addictive drugs, by H. S. Sugar, G. H. Mandell and J. Shalev. In a recent case report,[1] a rapidly progressive brain abscess was described in a heroin addict. The patient presented with an acute onset of unilateral weakness, dysphasia, hemaniopsia, and there were recent needle punctures in the anticubital fossa. At autopsy, phycomycosis was identified in necrotic brain tissue. The usual sino-orbital syndrome was absent and there was no pathologic evidence of the fungus in any other organ tissue. It is of particular interest that a consulting mycologist described stellate hairs in the tissue which might have represented remnants of the material used to purify the drug before injection. This report seems to lend support to the conjecture by Sugar and his associates that the fungal endophthalmitis in his patient was secondary to emboli from the injection site.

Fungal endocarditis is not uncommon in drug addicts, the most common organisms being Candida and Aspergila. In the absence of endocarditis one should be aware that fungal emboli from the drug injection site might well be the source of ocular as well as focal nervous system infections in this group of patients.

Stephen Hameroff
*Baltimore, Maryland*

### REFERENCE

1. Hameroff, S. B., Eckhardt, J., and Lindenberg, R.: Cerebral phycomycosis in a heroin addict. Neurology 20:261, 1970.

## BOOK REVIEWS

COLOUR ATLAS AND CRITERIA OF FUNDUS CHANGES IN HYPERTENSION. By Kimiho Irinoda. Tokyo, Igaku Shoin Ltd., 1970. Clothbound, 141 pages, table of contents, references, index, 89 color and 100 black and white figures. $19.00

A Japanese cooperative study of hypertensive retinopathy was started in 1961. In 1966 a committee composed of 14 Japanese ophthalmologists was organized to determine the diagnostic criteria for classifying the fundus changes in hypertension. This book represents a consensus of their work.

Diffuse and localized arterial narrowing, the arteriovenous ratio, variations in the width of the arterial light reflex, tortuosity, and arterial branching angulations were studied by means of retinal fundus photographs and measurements were made where possible. Examples of each type of change are illustrated by colored fundus photographs.

The classifications of Keith-Wagener, Wagener-Clay-Gipner, Scheie, and Leishman are then briefly summarized. A new and much more complicated classification is presented which is drawn mainly from Scheie, modified by their own findings. A similar modification of the Keith-Wagener classification is also presented.

The photographs are of such a quality that the changes exemplified cannot always be visualized, and there are no data presented indicating the hypertensive status of the patients photographed. The careful work of Stokoe and Turner (Brit. J. Ophth. 50:21, 1966), which demonstrates the unreliability of measuring arteriovenous ratios, has been ignored as has the effect of venous dilatation on these ratio measurements. In fact, the increasing venous changes, regularly present in both hypertension and arteriosclerosis of sufficient duration, and the secondary effect of venous insufficiency upon the arterial wall, have not been given consideration (see Fig. 22, p. 31; Fig. 23, p. 32; Fig. 24, p. 34; Fig. 29, p. 42).

Other figures (Fig. 72, p. 93; Fig. 73, p. 94; Fig. 76, p. 99 and Fig. 77, p. 100) are labeled as neovascularization in the retina or anastomosis of retinal vessels, whereas they are actually venous collaterals following branch veing obstructions.

Figure 87 (p. 113) may represent fluid beneath the retina or beneaath the pigment epithelium, but certainly not retinal edema as it is labeled, and Figure 61 (p. 80) is certainly a branch vein obstruction rather than obstruction of the central retinal vein.

It is too bad that Leishman's study was not given more weight, for it represents the first good clinicopathologic study of hypertensive retinopathy and includes systemic data as well.

I have some reservation regarding the results of cooperative studies in such a complicated area as hypertensive retinopathy. The cooperative study initiated by the American Ophthalmological Society resulted in the Wagener-Clay-Gipner classification which never gained widespread acceptance despite the labors and excellence of these highly qualified authors.

Finally, the English translation is not always perfectly clear.

George N. Wise

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CLINICAL EXAMINATIONS IN NEUROLOGY, 3rd ed. By members of the Departments of neurology, physiology, and biophysics of the Mayo Clinic. Philadelphia, W. B. Saunders, 1971. Clothbound, 350 pages, table of contents, index, 85 black and white figures, 1 color figure. $12.50

This compact volume contains a wealth of diagnostic information. It is a very valuable guide to the examination of a patient with neurologic history. An important section is devoted to an examination of infants and children. An anatomical organization

follows, covering the cranial nerves, neuro-ophthalmology, motor function, a sensory examination, mental, language and autonomic functions. Of further interest are diagnostic techniques involving the ancillary specialties such as neuroradiology, electroencephalography, electromyography, and spinal fluid examination.

The section on neuro-ophthalmology is probably of less interest to the ophthalmologist, who will likely derive such information from specialized ophthalmic texts. However, the neurologic examination is so clearly and concisely explained that this volume will be a worthwhile guide to the ophthalmologist.

Marcel Frenkel

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STEREOSCOPIC ATLAS OF CLINICAL OPHTHALMOLOGY OF DOMESTIC ANIMALS. By H. E. Jensen. St. Louis, C. V. Mosby, 1971. Clothbound, 201 pages, table of contents, index, 187 figures, 16 viewing reels and viewer, $49.50.

Veterinary ophthalmology has grown tremendously in this country. A year ago, the American Society of Veterinary Ophthalmology spawned the College of Veterinary Ophthalmology. It is anticipated that in the near future examinations will be made available for certification of veterinary ophthalmologists.

Dr. Jensen has thus written a timely and much needed atlas. Using the Donaldson stereo camera, the atlas has been heavily annotated with color View-Master stereoscopic photographs. The Mosby publishers have combined text material and stereo photographs in a complementary and easy to use fashion. The text begins with a chapter on instrumentation. It is evident that special instruments have not been designed for animal examination. Instead, the standard tools and methods are employed. The body of the book consists of a discussion of various disease entities organized into chapters on the basis of their location. The index is complete and contains the View-Master reel numbers to further facilitate use of the very fine color stereo photographs.

In the preface the author states that his is strictly a clinical approach and thus references to the available literature have been omitted. In point of fact, only Magrane's textbook of canine ophthalmology is given as a reference to the considerable ophthalmic veterinary literature. It is difficult to take such a position and not be criticized. We do, however, see post-therapeutic photographs which attest to the success of the author's therapeutic regimen. The descriptions and photographs of the diseases have been augmented by only five photomicrographs showing the histology. It must be remembered, however, that animal autopsy material may be as difficult to obtain as human material.

There are two outstanding chapters. The author's descriptions of corneal disease and of the many types of lens opacities are superior. The book clearly and concisely conveys one practitioners's vast clinical experience in veterinary ophthalmology. It is a valuable reference for the veterinarian with a busy practice.

J. Terry Ernest

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ADVANCE IN KERATOPLASTY. Edited by Nathaniel R. Bronson II and R. Townley Paton. Boston, Little Brown and Company, 1970. Clothbound, 268 pages, table of contents, index, 89 black and white figures. $25.00

The summer, 1970, issue of the International Ophthalmology Clinics deals with a course given in Southhampton. Its availability constitutes a sound lesson in the economy of subscribing to this series rather than purchasing an issue once it has proven its value.

Despite the title, the book deals with far more than keratoplasty. Dohlman, Lemp, and English describe the dry eye syndrome

and the methods of diagnosis of the various types. David Paton and Milauskas describe the results of thin conjunctival (Gundersen) flaps in 122 patients. Katzin, Elstein, and Sehgal describe a new keratome for use in refractive keratoplasty which they have not used clinically. Buxton inserted 64 Cardona-type keratoprostheses during 1962 and 1968; at that time 15% had been removed and 15% extruded. Much of the other work concerning the use of soft contact lenses, measurement of the intraocular pressure, and the postoperative period after keratoplasty, and the Mackay-Marg tonometer have already appeared in print, although they occasioned lively comment at the time of this meeting.

William F. Hughes

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THE FIRST CONGRESS OF THE INTERNATIONAL STRABISMOLOGICAL ASSOCIATION. Edited by Peter Fells. St. Louis, C. V. Mosby, 1971. Clothbound, 312 pages, table of contents, index of authors and index of subjects, 155 black and white figures.

The First Congress of the International Strabismological Association was held in March of 1970 with Keith Lyle presiding. Peter Fells has put the transactions of this meeting into a carefully edited and indexed book. The volume consists of three symposia and 20 papers.

The high point of the meeting was the honorary Bielschowsky Lecture given by Gunter von Noorden. This was a report of his subhuman primate studies on amblyopia done with John Dowling and Donald Ferguson. Unfortunately for this text, the papers have already been published. In fact, many of the papers presented at the meeting and organized into this textbook have been published separately. Nonetheless, the volume does represent a concentration of the latest clinical material. Furthermore, it has the considerable advantage of including the discussions following the presentations. In such a controversial field as strabismus, this fact alone makes the book of interest and value. The 41 participants represent some of the leading clinicians specializing in motility in this country and abroad. The first symposium, which was a discussion of early versus late surgery for strabismus, brought the clinicians "eyeball to eyeball." The panel agreed on the terminology for the time of surgery, but that is about all they agreed on. The most divergent views were those of Drs. Arruga of Barcelona and Parks of the United States. Dr. Parks presented data indicating that surgery between six and 18 months of age in the congenitally esotropic patient will result in a high percentage of single binocular vision with peripheral fusion, although not bifoveal fixation. Dr. Arruga stated that this result should be avoided since he believes that many of these children will develop osthenopic troubles by the time they reach school age. The panel emphasized the need for more statistics on both the immediate and long-term effects of early surgery. The second symposium was on the treatment of exodeviation and contained an excellent discussion by Dr. Bagolini on how he uses his striated glasses together with a graded bar of red filters. He pointed out that the correction of the deviation by prisms is a useful indicator for predicting diplopia. The panel agreed on the surgical treatment of intermittent and constant exotropia but there was a difference of opinion regarding the treatment of convergence insufficiency. Dr. Burian did not feel that convergence insufficiency is a true exodeviation and he would not operate on it. Dr. Knapp believes that once orthoptic exercises are stopped convergence insufficiencies become intermittent exotropias. Consequently he recommends resecting both medial rectus muscles. The final symposium on the use of prisms in strabismus also generated perhaps not unanticipated controversy.

The free papers, 20 in number, range from a description of a diplopia field tech-

nique to a discussion of microtropia. As is characteristic of contemporary strabismology, what are concrete data to one investigator may only be controversial observations to another.

There is a tremendous amount of information presented in these reports. The student who wishes to obtain a working knowledge of strabismus will benefit from a careful study of the papers. Further, a perusal of the material contained in this volume by the experienced clinician can only result in a healthy broadening of his information and attitudes toward the many approaches to the diagnosis and treatment of strabismus.

J. Terry Ernest

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OPHTHALMIC MINIATURE

The sensory equipment of the higher primates is much more dominated by the sense of vision than by the sense of smell. In their tree-climbing world, seeing well is far more important than smelling well, and the snout has shrunk considerably, giving the eyes a much better view. In searching for food, the colors of fruits are helpful clues, and, unlike the carnivores, primates have evolved good color vision. Their eyes are also better at picking out static details. Their food is static, and detecting minute movements is less vital than recognizing subtle differences in shape and texture.

Desmond Morris
*The Naked Ape*
Jonathan Cape, 1967

# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ACTA OPHTHALMOLOGICA

ELECTRON MICROSCOPIC DEMONSTRATION OF VIRUS PARTICLES IN HUMAN HERPES SIMPLEX KERATITIS. Nilsson, S. E. G. (Department of Ophthalmology, Karolinska Sjukhuset, Stockholm, Sweden), Acta Ophth. 48:76-85, 1970.

Electron microscopic studies of human corneal epithelium from patients with herpes simplex keratitis showed not only large numbers of virus particles in the areas of dendritic lesions but also fewer particles in the clinically undamaged cornea 2 to 5 mm away from the closest lesion. The author believes it to be due to a lower grade of infection and that dormant infection is the cause of recurrences. (5 figures, 21 references)—Saul Sugar

DENDRITIC (HERPETIC) KERATITIS. I. INCIDENCE, SEASONAL VARIATION, RECURRENT RATE, VISUAL IMPAIRMENT, THERAPY. Norn, M. S. (Department of Ophthalmology, Kommunehospitalet, Copenhagen, Denmark), Acta Ophth. 48:91-107, 1970.

A study of 109 patients with dendritic keratitis indicated the incidence to be 1:196 among all ophthalmic patients, 59% males. The first attack occurred most often in children or those between ages forty and fifty. Bilaterality was observed in 10%. No seasonal variations were found. Relapses occurred in 61%, the interval between the first and second attacks averaging 5.7 years. The recurrence rate was higher in I.D.U. treated patients but the course was milder, the final visual impairment being no different in the two groups. Steroids caused greater visual impairment. Iodine cautery had no influence on the recurrence rate. (6 tables, 34 references)—Saul Sugar

CHROMOSOMAL ANALYSIS OF A HUMAN RETINOBLASTOMA. Mark, J. (Department of Ophthalmology, University of Lund, Sweden), Acta Ophth. 48:124-135, 1970.

A study of the chromosomes of a sporadic human retinoblastoma patient revealed a well-defined hyperdiploid stemline and two small sidelines closely related to the stemline. No dilation of a D chromosome was present. Localization of the gene for development of retinoblastomas remains uncertain. (3 figures, 2 tables, 13 references)—Saul Sugar

THE ERG AND OPHTHALMOLOGICAL CHANGES IN EXPERIMENTAL METALLOSIS IN THE RABBIT. I. EFFECTS OF IRON PARTICLES. Knave, B. (Department of Physiology, Karolinska Institutet, Stockholm, Sweden), Acta Ophth. 48:136-158, 1970.

The eye changes and ERG were studied after implantation of pure iron particles into the vitreous in rabbit experiments. The particles were encapsulated in the first few days after implantation. After a week the capsule begins to resorb and the particles reappear after a time which depends on the size of the metal. About six months to a year later a thinner capsule develops. During the first phase after implantation there was a reversible reduction in a and b waves, a normal or slightly increased peak latency of the scotopic b wave and a moderate increase in the peak latencies of the oscillatory potential, all probably due to retinal edema. When the particles reappear there was a reduction of a and b wave amplitude and a marked increase of peak latencies of the oscillations. The b wave peak latency first decreased and later normalized. Later the potentials disappear. (11 figures, 1 table, 34 references)—Saul Sugar

THE ERG AND OPHTHALMOLOGICAL CHANGES IN EXPERIMENTAL METALLOSIS IN THE RABBIT. II. EFFECTS OF STEEL, COPPER AND ALUMINIUM PARTICLES. Knave, B. (Department of Physiology, Karolinska Institutet, Stockholm, Sweden), Acta Ophth. 48:159-173, 1970.

Eye changes and ERG were studied in rabbits after implantation of particles of steel, aluminium and copper. The implantation of steel particles gave results which depended on the alloys used. Steel alloyed with 5% nickel gave results similar to implantation of pure iron particles. Steel alloyed with 5% chromium gave a long-lasting reversible increase in ERG, the b more than the a wave. Later a small decrease occurred. When steel alloyed with 14% chro-

mium was implanted, a slowly developing small reduction of the ERG occurred. With steel alloyed with 18% chromium, 12% nickel and 3% molybdenum the ERG remained normal. In these three steel alloys only thin capsules developed. With aluminum implants there was a slow reduction of the b wave to none, the a wave to 90%, after 300 days. Only a thin partial capsule formed. With copper a rapid deterioration of the ERG occurred. Vitreal damage occurred rapidly. (5 figures, 9 references)—Saul Sugar

## American Journal of Medicine

G-6-PD Worcester: a new variant, associated with x-linked optic atrophy. Snyder, L. M., Necheles, T. F., Reddy, W. J., Calcagni, K. and Reed, F. (Saint Vincent Hospital, 25 Winthrop Street, Worcester, Massachusetts 01604), Amer. J. Med. 49:125-132, July, 1970.

A new variant of glucose-6-phosphate dehydrogenase (G-6-PD Worcester), is described in a caucasian family with associated congenital, nonspherocytic hemolytic anemia, absent erythrocyte G-6-PD activity and optic atrophy. The inheritance of this form of optic atrophy is closely linked to the G-6-PD locus and total color blindness. G-6-PD Worcester is distinguished from previously characterized variants by absent erythrocyte G-6-PD activity, slow electrophoretic mobility, thermolability, a sharp peak at pH 8 and a Michaelis constant for TPN of 11.2 micromolar. (5 figures, 3 tables, 33 references)—Authors' abstract

Benign cystinosis. Brubaker, R. F., Wong, V. G., Schulman, J. D., Seegmiller, J. E. and Kuwabara, T. (The Mayo Clinic, Rochester, Minnesota 55901), Amer. J. Med. 49:546-550, Oct., 1970.

Benign cystinosis is an autosomal recessive disorder characterized by the presence of cystine crystals in the eye and the bone marrow. There are no associated renal or peripheral retinal abnormalities which are typical of nephropathic cystinosis. Patients affected with the benign disorder are asymptomatic and presumably have a normal life expectancy. The youngest known patients, a girl aged eleven and a boy aged sixteen, are described. Biochemical and morphologic evidence suggests that in both forms of cystinosis storage of cystine occurs within the lysosomes, primarily of actively endocytic, mesodermally-derived cells. Although the two forms of cystinosis show points of similarity in the distribution of cystine crystals, they differ quantitatively in the amount of cystine accumulated, substantially less intracellular cystine being present in the benign than in the nephropathic form of the disorder. The abnormal gene products responsible for the accumulation of cystine in the two forms of the disease remain to be demonstrated. (2 figures, 2 tables, 18 references)—Authors' abstract

Familial nephropathy associated with retinitis pigmentosa, cerebellar ataxia and skeletal abnormalities. Mainzer, F., Saldino, R. M., Ozonoff, M. B. and Minagi, H. (University of California School of Medicine, San Francisco, California), Amer. J. Med. 49:556-562, Oct., 1970.

Two siblings were found to be affected by an oculorenal syndrome consisting of familial nephropathy and retinitis pigmentosa, and in addition two other extrarenal manifestations, cerebellar ataxia and skeletal abnormalities, not previously reported, were demonstrated in both patients. The renal abnormality in both siblings was characterized by functional defects of the distal tubules and collecting ducts, manifested by failure to concentrate and acidify the urine. The clinical and histologic findings were compatible with the nephropathy which is known as nephronophthisis or medullary cystic disease. (8 figures, 47 references)—Authors' abstract

Behcet's disease. Kalbian, V. V. and Challis, M. T. (Veterans Administration Center, Martinsburg, West Virginia 25401), Amer. J. Med. 49:823-829, Dec., 1970.

Twelve cases of Behcet's disease are presented, with a discussion of their main clinical features. The multiplicity of the clinical presentations of the disease is stressed. A new type of neurologic manifestation, that of benign intracranial hypertension, is introduced and three such cases are reported. (2 figures, 1 table, 37 references)—Authors' abstract

CATARACTS, GALACTOSURIA AND HYPERGALACTOSEMIA DUE TO GALACTOKINASE DEFICIENCY IN A CHILD. Monteleone, J. A., Beutler, E., Monteleone, P. L., Utz, C. L. and Casey, E. C. (St. Louis University School of Medicine, Missouri), Amer. J. Med. 50:403-407, Mar., 1971.

A nine year old girl with galactosuria, galactosemia and cataracts is described. She was found to have galactokinase deficiency. A large kindred was studied in detail and the disease was found to be autosomal recessive. In addition it is shown that carriers might be affected with cataracts early in life; for this reason we suggest that carriers adhere to a galactose-restricted diet. (3 figures, 1 table, 14 references)—Authors' abstract

## AMERICAN JOURNAL OF PSYCHIATRY

LONG-TERM TREATMENT WITH NEUROLEPTIC DRUGS AND EYE OPACITIES. Crane, G. E., Johnson, A. W. and Buffaloe, W. J. (Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Med.), Am. J. Psychiat. 127:1045-1049, Feb., 1971.

Approximately 100 chronic schizophrenic patients were examined for drug-induced eye changes. The lens was affected in 36 patients, the cornea in 19. There was a linear relationship between eye opacities and the total intake of drugs. Corneal opacities were also related to the intake of high doses of chlorpromazine over a short period of time. In most instances the ocular changes were irreversible. Despite heavy deposits in the anterior part of the eye, vision was unimpaired and the retina appeared to be intact. (2 tables, 14 references)—Authors' abstract

## AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

RADIOTHERAPY OF PRIMARY LYMPHOMA OF THE ORBIT. Foster, S. C., Wilson, C. S. and Tretter, P. K. (Department of Radiology, Columbia-Presbyterian Medical Center, New York, New York), Am. J. Roent. Rad. Nucl. Med. 3:343-349, Feb., 1971.

Thirty-three patients with primary lymphoma of the orbit were treated. Thirty had radiotherapy, and three had surgery alone as initial treatment. The results indicate that local control can be obtained and that in a significant percentage of patients the disease does not generalize. (2 figures, 4 tables, 13 references)—Joel G. Sacks

## ANNALI DI OTTALMOLOGIA E CLINICA OCULISTICA

OPTICO-CHIASMATIC ARACHNOIDITIS. CRITICAL REVIEW OF 108 SURGICAL CASES. (Italian) Migliore, A., Massarotti, M., Ettorre, G. and Bozzini, S. (University of Milan, Italy), Ann. Ottal. Clin. Ocul. 156:221-232, Apr., 1970.

Optico-chiasmatic arachnoiditis is a pathologic entity and not a syndrome. There are a variety of etiologies for this finding and no correlation can be made between the history and clinical findings and the pathologic process. There is no consistent visual field defect and encephalography offers very little additional information. The authors feel that over the years the indications for surgery have been restricted and that many of these cases can now be treated satisfactorily medically. (5 figures, 2 tables, 21 references)—David Shoch

## ANNALES D'OCULISTIQUE

STUDY OF THE CHIASMATIC SYNDROME IN THE COURSE OF PREGNANCY. (French) Bonamour, G., Bonnet, M. and Laffay, N. (Hopital de la Croix-Rousse, Lyon, France), Ann. Ocul. 204:235-256, Mar., 1971.

Bilateral, temporal field defects are sometimes seen in the course of pregnancy and it has been assumed that these might be due to a physiologic hypertrophy of the pituitary. The authors feel, on the basis of two cases reported, that it is more likely that a hypophyseal tumor is present in these cases and that it enlarges during pregnancy. If the tumor is discovered in the early months of pregnancy then a therapeutic abortion is advisable. On the

other hand, tumors discovered late in pregnancy can be treated neurosurgically without interruption of the pregnancy. (4 figures, 92 references)—David Shoch

DYSTROPHIC LESIONS OF THE HORIZONTAL RECTI IN COMITANT STRABISMUS. (French) Zolog, N. and Georgescu, L. (Timisoara, Romania), Ann. Ocul. 204:407-414, Apr., 1971.

The authors examined 15 musculo-tendinous fragments provided by 15 strabismic patients who underwent a resection of a horizonal rectus muscle. Histologic examinations of these fragments of tissue revealed an atrophy of muscle fibers, a homogenization of the sarcoplasma and the disappearance of nuclei and of striations. (7 figures, 11 references)—David Shoch

ACUTE GLAUCOMA SECONDARY TO INSTILLATION OF PILOCARPINE. (French) Francois, J., Goes, F. and Stockmans, L. (University of Gand, France), Ann. Ocul. 204: 481-490, May, 1971.

Open-angle glaucoma was diagnosed in a 65-year-old patient and he was treated irregularly with pilocarpine and Diamox. He was advised to use 2% pilocarpine regularly five times a day and the same evening that this treatment was started, he developed an acute angle closure in both eyes. It is felt that this was due to an anterior displacement of the lens due to a contraction of the ciliary body induced by the miotics and consequently a loosening of the zonular fibers. The result was a pupil block and angle closure. Dilatation of the pupil with epinephrine and intravenous mannitol cured the angle closure. (3 figures, 3 tables, 35 references)—David Shoch

## ARCHIV FÜR KLINISCHE UND EXPERIMENTELLE OPHTHALMOLOGIE

HYPERPLASIA OF THE ADVENTITIAL AND MURAL RETICULIN FIBERS IN DIABETIC RETINOPATHY. (German) Daicker, B. (Universitats-Augenklinik Basel), Arch. Klin. Exp. Ophth. 181:192-206, 1971.

The retinal vessels of diabetics, isolated by the trypsin digestion technique show a hyperplasia of the adventitial argyrophilic fibers on the medium-sized vessels and of the mesodermal strands. At the diabetic retinal capillaries a neoformation of mural argyrophilic fibers can be demonstrated as an early sign. A local hyperplasia of such fibers causes the formation of looping microaneurysms; the saccular aneurysms opposite these bulge and dilate the lattice of reticular fibers. This hyperplasia and neoformation of argyrophilic fibers is not pathognomonic for diabetic retinopathy, but is obviously marked and wide-spread in this affection. (10 figures, 1 table, 34 references)—Author's abstract

EXPERIMENTAL INVESTIGATIONS OF THE EFFECT OF GLYCERINE AND GLUCOSE SOLUTIONS UPON THE CORNEAL EDEMA. (German) Meyer, W. and Reinhardt, H. (Universitats-Augenklinik Jena, DDR), Arch. Klin. Exp. Ophth. 181:216-227, 1971.

Glucose and glycerine solutions reduce the thickness of the rabbit cornea to 50% of the original value. Glucose solutions show a more dehydrating effect on experimentally produced corneal edema than glycerine solutions of the same osmolarity. (9 figures, 23 references)—David Shoch

CALCULATION OF THE THERMAL EFFECT GENERATED IN THE RETINA BY PHOTOCOAGULATION. Roulier, A. (Universitats-Augenklinik, Bern, Switzerland), Arch. Klin. Exp. Ophth. 181:281-289, 1971.

The alterations of the retina produced by photocoagulation depend upon the temperature-time-history during and after exposure. A mathematical model is proposed enabling the calculation of a particular biological effect, namely the ophthalmoscopically visible white discoloration. . . . In agreement with experience the calculations show that for purposes of greatest energy efficiency and least damage to the nerve fiber layer, relatively small spot diameters (typically 0.2 mm) and exposure times of not more than a few milliseconds should be used in photocoagulation. (4 figures, 4 tables, 15 references)—Author's abstract

THE INTRAOCULAR TENSION AFTER RETINAL DETACHMENT SURGERY. (German) Uter-

mann, D. and Deichmann, C. R. (Universitats-Augenklinik Hamburg-Eppendorf), Arch. Klin. Exp. Ophth. 181:335-343, 1971.

The intraocular tension of 45 patients with retinal detachment was measured using applanation tonometry, directly pre- and postoperatively over a period of 14 days, with a final control after six months. It could be shown that the intraocular tension of eyes with retinal detachment lay on an average 1.45 mm Hg lower than that of normal eyes. An enormous increase in tension occurred post-operatively, which however always returned spontaneously to normal levels. On the 6th day the tension equalled that of the sound eye, but decreased to preoperative levels after the 12th day. Tonographic investigations showed no difference between either eye pre- or postoperatively. (4 figures, 1 table, 12 references)—Authors' abstract

## Archives of Neurology

ASSOCIATIVE VISUAL AGNOSIA. Rubens, A. B. and Benson, D. F. (Boston Veterans Administration Hospital, 150 S. Huntington Avenue, Boston 02130), Arch. Neurol. 24:305-316, Apr., 1971.

Following an acute hypotensive episode, a patient had unusual residual visual difficulties. A right homonymous hemianopsia was the only primary neurologic deficit, but there were specific behavioral disturbances. He could not read but could write (alexia without agraphia), had difficulty in color recognition (color agnosia), facial recognition (prosopagnosia), and object recognition (visual agnosia). Despite these visual disturbances, adequate primary visual function was demonstrated by his ability to copy drawings. Clinical evidence suggests that the underlying lesion was infarction involving the left medial occipital region and the splenium of the corpus callosum. The possibility of a second lesion in the right hemisphere can be conjectured but not supported by available data. Inability to identify or recognize visually presented objects with perservation of ability to draw them is unusual and can best be termed associative visual agnosia. (6 figures, 2 tables, 36 references)—Authors' abstract

## Archives of Ophthalmology

LIGHT DEPRIVATION FOR EARLY RETINITIS PIGMENTOSA. Berson, E. L. (Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston 02114), Arch. Ophth. 85:521-529, May, 1971.

Evidence is consolidated to support the hypothesis that long periods of almost complete light exclusion will have therapeutic benefit for patients with early stages of hereditary retinitis pigmentosa. The hypothesis is based on observations on effects of light on photoreceptors of normal rats and on photoreceptors of rats with either vitamin A deficiency or hereditary retinal dystrophy, on electrophysiological studies of patients with early retinitis pigmentosa, and on measurements of retinal oxygen utilization in humans and animals with retinal degenerations. Almost complete light exclusion can be best accomplished with an opaque flush-fitting scleral contact lens. If this hypothesis is correct and light exclusion is begun in the earliest stages, it may be possible to double the patient's visual lifetime by keeping one retina in reserve in darkness while the other retina functions but degenerates in light. (3 figures, 52 references)—Author's abstract

DOMINANT MICROSPHEROPHAKIA. Johnson, V. P., Grayson, M. and Christian, J. C. (Department of Medical Genetics, Indiana University, 1100 W. Michigan St., Indianapolis 46202), Arch. Ophth. 85: 534-542, May, 1971.

Microspherophakia, upward subluxation of the lens, myopia, retinal detachment, and inguinal hernias in various combinations were found in 11 individuals and three generations of one family. The mode of inheritance is compatible with a variable expressive dominant trait. There were no other stigmata of Marfan's or Marchesani's syndromes. The basic defect is postulated to be in mesodermal development, resulting in abnormal ciliary and globe development responsible for the myopia and microspherophakia and a milk connective tissue defect to account for the increased incidence of inguinal hernias. (6 figures, 3 tables, 35 references)—Authors' abstract

PSEUDOMONAS: CORNEAL ULCERS IN CONTACT LENS WEARERS. Golden, B., Finger-

man, L. H. and Allen, H. F. (University Hospitals, Iowa City 52240), Arch. Ophth. 85:543-547, May, 1971.

Pseudomonas species were associated with several corneal ulcers in two healthy young contact lens wearers. In both cases the source of contamination was traced to the patient's contact lens storage case. Cultures of wetting and soaking solutions in their bottles were negative. In both patients, the ulcers healed under treatment with specific antibiotics. In one case, topical corticosteroid and enzyme inhibitor therapy may have contributed to a successful result. (8 figures, 10 references)—Authors' abstract

CYCLODUCTION OF THE EYES WITH HEAD TILT. Linwong, M. and Herman, S. J. (University of Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago 60612), Arch. Ophth. 85:570-573, May, 1971.

In ten normal subjects a head tile of 30° to the same shoulder produced a mean incycloduction of 5° and a head tilt of 30° to the opposite shoulder produced a mean excycloduction of 6.5°. Similar results were obtained when the experiment was performed repeatedly on one eye in the same subject. (3 figures, 2 tables, 8 references)—Authors' abstract

CORNEAL TEMPERATURE MEASUREMENTS DURING RETINAL PHOTOCOAGULATION. de Guillebon, H., Pfister, R., Govignon, J., Pomerantzeff, O. and Schepens, C. L. (Retina Foundation, 100 Charles River Plaza, Boston 02114), Arch. Ophth. 85: 712-717, June, 1971.

The corneal temperature elevation of 30 rabbits were measured with thermocouples during a series of retinal photocoagulations. Topical saline irrigation substantially reduced final temperature levels. The head distribution over the illuminated cornea showed higher values centrally. Major temperature rises developed when the pupil was smaller than the cross section of the light beam. With a contact lens, temperature elevation is greatest and may reach 8 C for small pupillary apertures. To avoid high corneal temperatures during clinical photocoagulation, especially with a contact lens, frequent saline irrigations, a beam diameter smaller than the dilated pupil, and long intervals between the photocoagulation applications are required. (8 figures, 5 references)—Authors' abstract

CHRONIC ANGLE-CLOSURE GLAUCOMA. Pollack, I. P. (Wilmer Institute, Johns Hopkins University School of Medicine, 601 N. Broadway, Baltimore 21205), Arch. Ophth. 85:676-689, June, 1971.

Twelve persons with asymptomatic chronic glaucoma and extremely narrow anterior chamber angles that appeared open were treated successfully with peripheral iridectomy. In each case initial examination revealed that there were no symptoms of angle closure and the clinical picture strongly resembled chronic (simple) open-angle glaucoma; intraocular pressure was elevated and frequently aggravated by medical therapy; there were large fluctuations in intraocular pressure; the angle was open to a slit or grade 1, except in one case with partial angle closure; and the mydriatic provocative test was negative. The natural course in this disease is for the chamber angle to become progressively narrowed with eventual appositional closure and later formation of peripheral anterior synechias. If the disease process is interrupted before formation of synechias, then the glaucoma is cured or can be controlled easily. (13 figures, 2 tables, 14 references)—Author's abstract

## AUSTRALIAN ANNALS OF MEDICINE

LEBER'S OPTIC ATROPHY: A POSSIBLE EXAMPLE OF VERTICLE TRANSMISSION OF A SLOW VIRUS IN A MAN. Wallace, D. C. (Queensland Institute of Medical Research, Brisbane, Australia), Aust. Ann. Med. 3:259-262, 1970.

The unusual inheritance of Leber's disease could be caused by the presence of a slow virus acting upon individuals with a variable and partly inherited resistance to infection. A study of a family afflicted by Leber's disease is presented and shows a pattern strongly suggestive of vertical transmission. As usual, no man passed the disease on to his descendents. Affected women and unaffected carriers are considered to pass on the infection to all of

their children, the degree of expression depending upon the virulence of the virus and the resistance of the child. (1 figure, 14 references)—Ronald Lowe

## British Journal of Ophthalmology

SUPERIOR OBLIQUE TENDON SHEATH SYNDROME. AN ELECTROMYOGRAPHICAL STUDY. Catford, G. V. and Dean Hart, J. C. (6 Devonshire Place, London), Brit. J. Ophth. 55:155-160, Mar., 1971.

Electromyographic studies were done on three patients with a superior oblique tendon sheath syndrome. In all these cases there was normal firing although of smaller amplitude than from the inferior obliques. There was no evidence of co-contraction or abnormal innervation and therefore the authors conclude that the superior oblique tendon sheath syndrome is due to a local mechanical problem caused by the inability of the tendon to pass freely in its full extent through the sheath. (9 figures, 16 references)—David Shoch

LOWERING OF INTRAOCULAR PRESSURE IN THE UNTREATED EYE AFTER THE USE OF TOPICAL STEROIDS. Das, S. N. and Hitchings, R. A. (Moorfields Eye Hospital, City Road, London), Brit. J. Ophth. 55: 161-164, Mar., 1971.

The authors studied a group of patients whom they divided into responders and nonresponders. They show that when steroids are introduced into one eye of responders there is an increase in intraocular pressure in the second eye. On the other hand, in the nonresponder group, there was a lowering of the pressure in the untreated eye. The authors feel that these phenomena are explained by systemic absorption of the steroids from the culde-sac and its humoral effect on the second eye. (1 table, 24 references)—David Shoch

RETINAL VASCULAR OCCLUSION AS A PRESENTING FEATURE OF GLAUCOMA SIMPLEX. Soni, K. G. and Woodhouse, D. F. (Wolverhampton and Midland Counties Eye Infirmary, England), Brit. J. Ophth. 55: 192-195, Mar., 1971.

The etiology, incidence and treatment of simple glaucoma in retinovascular occlusion are discussed in relation to a clinical series. Twenty-five percent of patients with central retinal venous occlusion had glaucoma, but only 8.6% of those with tributary venous occlusion. It is emphasized that the diagnosis of simple glaucoma should be considered in all patients presenting as a retinal vacular accident. (2 tables, 11 references)—Authors' abstract

PITUITARY GLAND ABLATION BY $^{90}$YTTRIUM IMPLANTATION FOR ADVANCING DIABETIC RETINOPATHY. Cullen, J. F., Gibson, P. F., MacCuish, A. C., Harris, P., Donaldson, A. A., Munro, J. F. and Duncan, L. F. (Princess Alexandra Eye Pavilion, Chalmers St., Edinburgh), Brit. J. Ophth. 55: 217-224, Apr., 1971.

The authors report the results of pituitary ablation by 90 yttrium implantation for advancing diabetic retinopathy. Of the 20 patients, seven were dead by the end of four years, either as a complication of the surgery or as a complication of their diabetes. Cerebrospinal fluid rhinorrhea occurred in three patients. Ten of the patients are reported as having an arrested retinopathy while four improved. The authors acknowledge that peripheral areas of neovascularization can be effectively eradicated by photocoagulation but they feel that pituitary ablation is the best treatment for neovascularization of the optic nerve head. However, recent data has shown that even these areas may be treated with the new argon laser. (5 tables, 14 references)—David Shoch

TRAUMATIC OPTIC PATHWAY DEGENERATION. Kurz, G. H., Ogata, J. and Gross, E. M. (Hunterdon Medical Center, Flemington, N.J.), Brit. J. Ophth. 55:233-242, Apr., 1971.

A 45-year-old man had been totally blind following a gunshot wound which injured both optic nerves nearly 13 years previously. Post mortem examination revealed degenerative changes in the injured neurons (retinal ganglion cells and distal and proximal stumps of their axons) as well as antegrade trans-synaptic degeneration (lateral geniculate body) and retrograde trans-synaptic degeneration (inner nuclear layer). A macular hole and a chorioretinal scar were also present in one eye. The retinal vascular pattern remained intact. (11

figures, 1 table, 14 references)—Authors' abstract

RETINAL HEMORRHAGES IN NEWBORN INFANTS. Sezen, F. (Capa Goz Klinigi, Capa, Istanbul, Turkey), Brit. J. Ophth. 55:248-253, Apr., 1971.

Of 1,238 newborn infants investigated, 178 (14.3%) were affected. Examination within 24 hours revealed a percentage of 18.9 but between the third and fifth day the figure was only 2.6%. It is concluded that the later the time of fundus examination the less the incidence of retinal hemorrhage found. Comparative studies of the incidence and etiology of retinal hemorrhages have shown that the difference between primiparae and multiparae is significant (P 0.002); retinal hemorrhages were more common in the babies of primiparae, confirming the role of obstetric trauma in the pathogenesis of neonatal retinal hemorrhages. (4 tables, 25 references)—Author's abstract

EXPERIMENTAL ASTEROID HYALOPATHY. Lamba, P. A. and Shukla, K. N. (Jawaharlal Institute of Post-Graduate Medical Education and Research, Pondicherry, India), Brit. J. Ophth. 55:279-283, Apr., 1971.

Experiments were carried out to ascertain whether the ingestion of cholesterol by animals could produce visible vitreous bodies (asteroid hyalitis). On the basis of our investigations and the reports of earlier workers, it may be supposed that hypercholesterolemia per se is not the principal factor in the development of asteroid bodies. Local causes may result in the precipitation of macroscopically visible particles of calcium and cholesterol (normal constituents of vitreous). To investigate the role of local changes in the vitreous, hyaluronidase enzyme was injected into the vitreous humour; this produced white, angular, discrete particles which were clinically and microscopically similar to those seen in asteroid hyalopathy. (2 figures, 12 references)—Authors' abstract

ELECTRON MICROSCOPICAL STUDY OF COATS'S DISEASE. Tripathi, R. and Ashton, N. (Institute of Ophthalmology, Judd St., London $WC1H_9QS$), Brit. J. Ophth. 55: 289-301, May, 1971.

An ultrastructural study of an early case of Coats's disease confirms the widely-held view that an abnormal permeability of the retinal vessels is fundamental in its pathogenesis. It is suggested that the pathological changes may initially derive not from telangiectasis, but from a functional or structural breakdown of the blood-retinal barrier (vascular endothelium), giving rise to plasmatic vasculosis and mural disorganization, and that these result in aneurysmal dilations and telangiectasis. Leakage of blood components then increases to form intraretinal and subretinal exudates, hemorrhages, lipid and fibrin deposits, with phagocytic proliferation, disorganization and destruction of the retinal elements, and eventually glial and fibrous tissue organization. The characteristic profusion of macrophages and "ghost cells" within the affected areas is most likely due to the local proliferation of resting histiocytes in the retina itself, augmented by blood-borne macrophages and migrating pigment epithelial cells. (17 figures, 26 references)—Authors' abstract

## INVESTIGATIVE OPHTHALMOLOGY

COLOR VISION: AN APPROACH THROUGH THE CONE PIGMENTS. Rushton, W. A. H. (Institute of Molecular Biophysics, Florida State University, Tallahassee), Invest. Ophth. 10:311-321, May, 1971.

There are three types of cone in the human retina, one containing erythrolabe, one chlorolabe, and one cyanolabe. . . . Protanopes, deuteranopes, and tritanopes simply lack the erythrolabe, the chlorolabe, or the cyanolabe sensitivity curves (respectively). . . . Color appearance depends (1) upon the quantum catch in the cones and (2) upon the processing of the resulting nerve signals. The first is extremely simple, the second extremely hard to comprehend exactly. Any two colors whose quanta are caught equally by each of the cone pigments will appear identical whatever may be the state of the nerve processing (adaptation, contrast, etc.), for, colors matched at input must also match at output however complex and adaptable that output may be. (6 figures, 20 references)—Author's abstract

THE EFFECT OF HYPOXIA ON VISUAL FUNCTION. PSYCHOPHYSICAL STUDIES. Ernest, J. T. and Krill, A. E. (Eye Research Laboratories, University of Chicago, Illi-

nois), Invest. Ophth. 10:323-328, May, 1971.

Hypoxia raised both cone and rod absolute visual thresholds. However, cone thresholds were elevated to a greater degree than rod thresholds at a 5° retinal eccentricity where both were studied. Hypoxia had a greater effect on peripheral rod thresholds (measured at 45° eccentricity) than on central rod thresholds (measured at 5° eccentricity). Only the later portions of rod and cone dark adaptation curves were affected by hypoxia. The first four minutes of either type of curve was unaffected. (2 figures, 3 tables, 23 references) —Authors' abstract

## LANCET

SMALL BLOOD-VESSELS IN MIGRAINE. Blau, J. N. and Davis, E. (National Hospitals for Nervous Diseases, Queen Square, London W.C. 1), Lancet 2:740-742, 1970.

Conjunctival, lip, tongue, and nailfold vessels have been examined microscopically in 35 migrainous subjects between attacks. The vessels were normal, but 12 out of the 35 showed intravascular red-cell aggregation (I.R.C.A.) —a substantially higher proportion than in controls. Eleven subjects were also photographed during attacks of migraine: conjunctival arterioles, capillaries, and venules became constricted in six and dilated in five. The vasomotor responses were invariably bilateral, although more distinct on the headache side. During attacks all subjects showed I.R.C.A.; and, where this feature had been present between episodes, the aggregation became more pronounced. The conjunctiva became edematous in 3 of the 11. Seven patients were observed in more than one attack and the vascular response remained the same in the particular subject. No changes were observed in tongue vessels. Lip and nailfold vessel responses fell within the normal range of "spontaneous" vasomotor variation. The vascular responses in migraine are bilateral; the headache may be associated with conjunctival vasoconstriction or vasodilatation; edema of the conjunctivae can occur with either vascular response; and the symptoms and the anatomical derivation of the conjunctival vessels support the view that an intracranial component contributes to the pain of a migraine headache. (2 figures, 14 references)—Authors' abstract

PLASMA-COBALAMINS IN NEURO-OPHTHALMOLOGICAL DISEASES. Wilson, J., Linnell, J. C. and Matthews, D. M. (Institute of Neurology, London W.C. 1), Lancet 1: 259-261, 1971.

Plasma-cyanocobalamin levels were found to be significantly raised in Leber's hereditary optic atrophy, dominantly inherited optic atrophy, tobacco amblyopia, and sporadic cases of optic atrophy. This change may be evidence of inborn metabolic errors of cyanide detoxication, varying clinically and genetically according to the particular enzyme involved. (3 tables, 1 figure, 17 references)—Authors' abstract

## NEW ENGLAND JOURNAL OF MEDICINE

PUPILLARY EFFECTS OF LEVODOPA THERAPY. Weintraub, M. I., Gaasterland, D. and Van Woert, M. H. (Yale-New Haven Hospital, New Haven, Conn. 06510), N. Eng. J. Med. 283:120-123, 1970.

In a patient with Parkinson's disease and subclinical postganglionic Horner's syndrome anisocoria developed during chronic oral L-dopa therapy. This provided an opportunity to investigate the mechanism of action of L-dopa and dopamine on the sympathetic innervation of the eye. Five patients, one of whom had a postganglionic Horner's syndrome without Parkinson's disease, served as controls. Topical dopamine and chronic systemic L-dopa produced pupil dilatation only in eyes with intact sympathetic innervation. Single large doses of L-dopa had no effect on the pupil size. L-dopa and topical dopamine appear to produce pupillary dilatation indirectly, through a peripheral increase in activity of intact sympathetic pathways, and not through direct alpha-receptor stimulation. (6 figures, 14 references)—Authors' abstract

RETINOBLASTOMA: EPIDEMIOLOGIC CHARACTERISTICS. Jensen, R. D. and Miller, R. W. (National Cancer Institute, 402 Wiscon Bldg., Bethesda, Md. 20014), N. Eng. J. Med. 285:307-311, 1971.

Nationwide study of 269 death certificates for United States children with retinoblastoma,

1960-67, revealed a peak in mortality at two to three years of age that was 2½ times greater in Negroes than in whites. Nationally, an estimated 81% of children with the neoplasm survived. Study of 1623 hospital records of children with retinoblastoma revealed an excess of mental retardation: 21 cases observed vs. 4.7 expected. Associated malformations in several cases suggested D-deletion syndrome, which has been described by others in six children with retinoblastoma. In accord with previous studies, radiotherapy was associated with an excess of osteosarcoma, soft-tissue neoplasms or carcinoma of the skin. In addition, 11 children had secondary primary cancers not attributable to radiotherapy, a seeming excess over normal expectation. The cell types were diverse, but three were osteosarcomas, suggesting an innate susceptibility that may add to the risk of radiotherapy. (1 figure, 3 tables, 28 references)—Authors' abstract

## Ophthalmic Research

On endocrine orbitopathy. Dardenne, M. U., Poonawalla, N. H., Hanrath, P. and Nocker, D. (University of Bonn, Bonn), Ophth. Res. 1:344-353, 1970.

From previous clinical and experimental observations with animals it is clear that the exophthalmos producing factor (EPF) is not the only factor which is responsible for endocrine orbitopathy. Therefore, a study of the effect of ACTH, cortisol, adrenaline, testosterone, oestradiol and oestriol on experimental exophthalmos in fish was made. Preliminary investigations were also made with a view to finding the most suitable medium of administration of drugs to goldfish and the minimum quantity of EPF that can produce a definite exophthalmos. Two doses of 0.25 mg TSH in 0.7% sodium chloride solution were found to be most suitable for obtaining a minimum but definite exophthalmos. TSH in combination with ACTH and testosterone had a synergistic effect while oestradiol and cortisol were found to inhibit the action of EPF. Adrenaline produced exophthalmos which lasted for a short time; this effect is probably due to its vasoconstrictor action. Progesterone produced exophthalmos and in combination with EPF, their effects were additive. These results show that disturbances in the regulation of different hormones can produce endocrine orbitopathy. (7 figures, 14 references)—Authors' abstract

## Ophthalmologica

Abnormal findings in relatives of patients with juvenile hereditary macular degeneration (Stargardt's disease). Merin, S. and Landau, J. (Department of Ophthalmology, Hadassah University Hospital, Jerusalem), Ophthalmologica 161:1-10, 1970.

A search for ocular anomalies in a family with two cases of typical Stargardt's disease (two brothers, aged 15 and 23) revealed in the apparently healthy mother and in one maternal aunt the peripheral manifestations of the dystrophy without involvement of the central area. (9 figures, 13 references)—Peter C. Kronfeld

Regarding hemorrhages and venous stasis associated with drusen of the optic disc. (German) Otradovec, J. and Vladyková, J. (Second University Eye Clinic and Eye department of the Central Military Hospital in Prague), Ophthalmologica 161:21-30, 1970.

Close observation of patients with drusen of the optic disc reveals phases of bleeding into and under the retina and of venous stasis confined to one or two vessels. These ophthalmoscopic changes suggest activity of the process of drusen formation which is most typically observed in young people. (5 figures, 8 references)—Peter C. Kronfeld

Unstable fixation and vertical nystagmus. (French) Jeannerod, M. (Laboratory for Experimental Medicine, Faculty of Medicine, Lyon), Ophthalmologica 161:31-37, 1970.

In ten patients with diffuse brain stem disease (multiple sclerosis or tumor) the electrooculograms revealed instability of fixation in the form of horizontal saccades which increased in amplitude with reduced illumination and became associated with a vertical nystagmus. These saccades probably represent the same phenomenon as the "flutter-like oscillations" described by Cogan and others as specific signs of cerebellar disease. (4 figures, 12 references)—Peter C. Kronfeld

Occlusion amblyopia. Keiner, E. C. J. F.

(Zwolle, The Netherlands), Ophthalmologica 161:55-62, 1970.

The relationship between occlusion amblyopia and changes in fixation pattern was studied in five cases of convergent strabismus. Two processes may be recognized in the effect of constant occlusion of the fixating eye in cases of strabismic amblyopia, namely, 1) a shift in fixation from the originally fixating eye to the amblyopic eye, and 2) an improvement in acuity of the amblyopic eye and a drop in acuity in the originally fixating eye, both starting at the time of the shift in fixation. The younger the child, the faster is the drop in acuity in the originally fixating eye. Through occlusion of the other eye, the originally fixating eye regains normal acuity very rapidly, even before dominant fixation position has been restored. (10 references)—Peter C. Kronfeld

BILATERAL RECURRENCE OF SALZMANN'S DYSTROPHY AFTER PERFORATING KERATOPLASTY. (French) Houber, J.-P. (University Eye Clinic Geneva, Switzerland), Ophthalmologica 161:90-97, 1970.

The eyes of a 71-year-old female patient became available at autopsy six and 24 years, respectively, after keratoplasty. The dystrophy had slowly extended into the graft. The histologic findings are described in detail. On the basis of these findings large lamellar grafts are considered most suitable for cases of Salzmann's nodular dystrophy. (6 figures, 11 references)—Peter C. Kronfeld

OCULAR CHANGES IN PATIENTS ON LONG-TERM CHLORPROMAZINE THERAPY. (German) Kalberer, M., Atar, Z. and Bider, E. (University Eye Clinic Basle, Switzerland), Ophthalmologica 161:118-124, 1970.

The total dose of chlorpromazine in this series of 22 psychiatric patients ranged from 79 to 1685 grams, the daily dose from 50 to 1600 mg. Aside from the now well-known corneal and lenticular changes, the only signs of ocular toxicity were subnormal or definitely pathologic EOGs. (1 table)—Peter C. Kronfeld

CORTISONE CATARACT AFTER KIDNEY TRANSPLANTATION. (German) Rintelen, F. and Dobrivojevic, D. (University Eye Clinic Basle, Switzerland), Ophthalmologica 161:125-131, 1970.

The development of cataracts was observed in seven out of 11 patients treated with prednisone and azathioprine to suppress immune reactions after kidney transplantation. The large doses of prednisone that had to be used and the early biomicroscopic picture of the cataract spoke for its being caused by the corticosteroid. In the discussion Kern (Zürich) reported the occurrence of cataract in 15 out of 29 patients treated with prednisone and azathioprine after kidney transplantation. The survival period of the patients without cataract was significantly shorter than that of patients with cataracts. In addition to posterior and anterior saucer-shaped opacities Kern observed in his series fleck-shaped, densily opaque areas resembling Vogt's glaucoma flecks. The possibility of their being related to the azathioprine medication was considered. (1 figure, 1 table)—Peter C. Kronfeld

REGARDING THE TREATMENT OF MALIGNANT EXOPHTHALMOS. (German) Della Casa, F. (Burgdorf, Switzerland), Ophthalmologica 161:145-151, 1970.

A case of malignant exophthalmos in a middle-aged female patient which had apparently progressed on 60 to 100 mg of prednisone and 60 to 80 mg of carbimazole per day, slowly improved on retrobulbar depo-Medrol and smaller doses of carbimazole. (2 figures, 2 references)—Peter C. Kronfeld

THE DETERMINATION OF THE RETINAL VISUAL ACUITY IN THE PRESENCE OF CATARACT. (German) Goldmann, H. and Lotmar, W. (University Eye Clinic Berne, Switzerland), Ophthalmologica 161:175-179, 1970.

The authors have tested the resolving power of the retina by means of interference fringes of varying fineness. Interference fringes are virtually independent of the optical characteristics of cornea and lens; stray light due to optical imperfections reduces the contrast (the amplitude) of the pattern, but does not change its fineness (the number of cycles per degree of visual angle). For the production of interference fringes on the retina the authors first used a Michelson-interferometer. In five normal subjects with geometric-optical (or Snellen-) acuities of 1.0 (equaling 1′ of

resolution), the retinal resolving power as measured with interference fringes was only 2′ which the authors attribute to entoptic phenomena and to the large size of their test-field. In four cases of far-advanced cataracts with finger counting or less geometric-optical vision no interference acuity could be measured. In another group of six eyes with cataracts and geometric-optical acuities ranging from LP and P to 0.2, the patients were able to find a position of their heads (that is, relatively clearer portions of their lenses) in which very much better interference acuities could be recorded; these were confirmed by good geometric-optical acuities after the removal of the cataract.

In their most recent work the authors have used an adaptation of the illuminating system of the Haag-Streit #360 slit lamp for the production of retinal interference fringes. (1 figure, 3 tables, 6 references)—Peter C. Kronfeld

VISUAL EVOKED RESPONSE OF THE VISUAL CORTEX IN MACULA DEGENERATIONS. (German) Bider, E. (University Eye Clinic Basle, Switzerland), Ophthalmologica 161:187-195, 1970.

With stimuli of 110 mL in a 2° centrally fixated test field the author has obtained visual evoked responses which were definable in terms of latent period, amplitude and number of waves. In visually normal individuals the latency period ranged from 40 to 60 msec, the amplitude of the first wave from eight to 35 $\mu$V and the differences between right and left eye from one to three $\mu$V. In 16 patients with various types of macula lesions there was a fair degree of correlation between visual acuity and the visual evoked responses. The author considers his method particularly suitable for testing small foveal lesions. (5 figures, 1 table, 30 references)—Peter C. Kronfeld

THE ERG IN BEHÇET'S DISEASE. (German) Kožoušek, V. (University Eye Clinic and Canton-Hospital Zürich, Switzerland), Ophthalmologica 161:196-201, 1970.

Five cases representing a wide range of stages of the disease were examined under photopic and scotopic conditions. The findings were similar to those in tapeto-retinal degenerations, but still sufficiently different to be useful in the differential diagnosis. (3 figures, 1 table, 6 references)—Peter C. Kronfeld

EPIRETINAL FIBROPLASIA AND MASSIVE PRERETINAL RETRACTION. (German) Gloor, B. P. (Department of Ophthalmology, Washington University, St. Louis), Ophthalmologica 161:227-236, 1970.

Previous experimental work aiming at elucidation of the mechanism of epiretinal fibroplasia following photo- or diathermy-coagulation is reviewed. The cells involved in the fibroplasia are predominantly hyalocytes. Their proliferation occurs in areas in which cell-containing vitreous is normally present or has been left behind after detachment of most of the vitreous. This explains the occurrence of macular puckering after coagulations in the periphery. Regarding treatment, steroids in massive doses started at the very beginning of the process may be beneficial. Prophylactically, it seems important to use only non-perforating coagulations and to wait as long as possible before repeating them. (31 references)—Peter C. Kronfeld

CLINICAL EXPERIENCES WITH HYDROPHILIC CONTACT LENSES IN UNILATERALLY APHAKIC CHILDREN. (German) Dreifus, M. (University Eye Clinic Zürich, Switzerland), Ophthalmologica 161:279-285, 1970.

Between 1963 and 1969, 88 unilaterally aphakic children were fitted with hydrophilic (soft) contact lenses. The ages of the children ranged from two to nine years, the period of uncorrected aphakia from one month to more than a year. Thirty-seven of the 88 children became regular contact lens wearers for a minimum of six to eight hours per day. The others wore the lenses only occasionally for which the author blames the parents. Irregularities in the shape and transparency of the cornea accounted for better contact lens than spectacle lens acuity in a significant number of children. Despite the good visual acuity, 54% of the eyes corrected with contact lenses remained in exotropia. (6 figures)—Peter C. Kronfeld

THE TREATMENT OF EPITHELIAL INVASION OF THE ANTERIOR CHAMBER AFTER CATARACT OPERATION. (German) Witmer, R.

(University Eye Clinic Zürich, Switzerland), Ophthalmologica 161:286-291, 1970.

From experiences in eight cases of epithelial downgrowth and five cases of postoperative iris cysts the author strongly recommends early surgical treatment which, in the case of epithelial downgrowth, consists of reopening of the original incision, excision of the affected iris and careful curettage of the affected cornea. (6 references)—Peter C. Kronfeld

FOLLOW-UP AND LATE RESULTS AFTER OPERATIONS FOR CANALICULUS OBSTRUCTION. (German) Huber, P. and Benz, G. (Eye Clinic of the Canton-Hospital St. Gallen, Switzerland), Ophthalmologica 161:313-323, 1970.

The operations under discussion are Bangerter's lacodacryostomy which is an anastomosis between the lower-nasal fornix and the lacrimal sac, and Bangerter's lacoductostomy which is an anastomosis between the lower-nasal fornix and the nasolacrimal duct, with a connecting channel made out of buccal mucous membrane. About 20 days after the operation a piece of rubber tubing is inserted into the surgically created passages which is replaced, two to three weeks later, by a custom-made, individually fitted plastic probe. Probes of the latter type are worn, with changes about every four to five months, for a total of about two years. A fairly common postoperative complication is the formation of a conjunctival fold which blocks the beginning of the surgically created passage. These folds are usually removed surgically. About half of the patients operated upon report complete comfort. (5 figures)—Peter C. Kronfeld

THE OCULAR SIGNS OF LESIONS OF THE CAROTID ARTERY. (French) Babel, J., Gauthier, G., Psilas, K., Ricci, A., Soriano, H. and Tsacopoulos, M. (University Eye Clinic Geneva, Switzerland), Ophthalmologica 161:324-339, 1970.

The paper deals with correlations between arteriographic findings (carotid artery or aortic arch arteriography) and the pressure in the ophthalmic artery (as estimated by ophthalmodyamometry) and arm-retina circulation time in patients with stenoses or thromboses of one or both carotid arteries. In general, the ophthalmic artery pressure estimates correlated better with the arteriographic findings than the arm-retina circulation times. (8 tables, 17 references)—Peter C. Kronfeld

THE CHOICE OF SURGICAL TREATMENT IN V-PATTERN ESOTROPIA. (French) Deller, M. and Brack, B. (University Eye Clinic Lausanne, Switzerland), Ophthalmologica 161;340-345, 1970.

The authors report on a series of 40 children with V-pattern esotropia, 34 of which were less than two years old. The operation consisted of symmetrical recessions of both medial recti and myotomies of both inferior obliques, all done in the same sitting. The incomitance, that is, the V-pattern esotropia was eliminated in 85% of the cases. Some measure of binocular vision was obtained in 62.5% and a good cosmetic result without gain in binocular vision in 22.5% of the cases. A second operation yielded two more good cosmetic results and two failures. Added to horizontal muscle surgery, the inferior oblique myotomies gave decidedly better results than the previously used tucking of the tendons of the superior obliques. (7 references)—Peter C. Kronfeld

BERTALANFFY'S METHOD FOR THE DEMONSTRATION OF TUMOR CELLS IN THE BLOOD OF PATIENTS WITH OCULAR TUMORS. (German) Goder, G. and Velhagen, K.-H. (Eye Clinic of the Humboldt University, Charité, Berlin), Ophthalmologica 161: 372-384, 1970.

The method devised by Bertalanffy is based upon yellow to brown fluorescence emitted by cells with increased protein synthesis after treatment with acridine-orange. In the circulating blood megakaryocytes, endothelial cells and malignant tumor cells may show this type of fluorescence. The test was clearly positive in ten, doubtfully positive in four and negative in four cases of histologically verified cases of malignant melanoma of the uvea. The difficulties and the potential sources of error of the method are stressed. (6 figures, 1 table, 17 references)—Peter C. Kronfeld

THE ASSOCIATION OF LEBER'S CONGENITAL AMAUROSIS WITH STIGMATA OF OCULAR ALBINISM. (French) Holland, M. G. and

Cambie, E. (Department of Ophthalmology, Tulane University, New Orleans, La.), Ophthalmologica 161:425-436, 1970.

An apparently sporadic case of typical congenital amaurosis in a 5-year-old boy was found to have translucent irides. His mother showed translucent irides and the characteristic fundus picture of the carrier of albinism. Her father's eyes were normal except for translucent irides. (6 figures, 50 references)—Peter C. Kronfeld

THE OPTIMAL AGE FOR SURGERY IN STRABISMUS CONVERGENS AND SURSOADDUCTORIUS. (German) Ditzen, K., Grützner, P., Immich, H. and Mattheus, S. (University Eye Clinic Heidelberg and Institute for Documentation, Information and Statistics of the German Cancer Research Center), Ophthalmologica 161:466-476, 1970.

This is a statistical evaluation of the effect on the angle of squint of 3.5 mm recessions of both medial recti or 10 to 15 mm myectomies of one or both inferior obliques. The measurements were made with the prism-cover test 4 to 5 days and in half of the cases, one year after the surgery. The effect of the medial rectus recessions was found to diminish markedly if the child was over six years old at the time of surgery. The effect of the inferior oblique surgery did not appear to be related to the child's age at the time of the operation. (2 tables, 3 references)—Peter C. Kronfeld

THE EXTENT OF THE ACCOMMODATION PHOSPHENE IN THE VISUAL FIELD. (German) Comberg, D. (Eye Clinic of the Charité, the Humboldt-University Berlin), Ophthalmologica 161:499-503, 1970.

The study was prompted by the apparent relationship between the use of strong miotics and the onset of retinal detachments. Purkinje in 1825 described a phosphene associated with accommodation in the completely dark adapted eye which takes the form of a bluish-white ring in the periphery of the visual field. The present author found the inner border of the phosphene to lie between 45 and 55 degrees of eccentricity. The retinal zone peripheral to this border is apparently under the mechanical influence of the ciliary muscle during accommodation. Most retinal breaks lie in that area. A causal relationship between ciliary muscle contraction and retinal atrophy is possible. (2 figures, 11 references)—Peter C. Kronfeld

## PEDIATRICS

ADRENERGIC NEURONE AND RECEPTOR ACTIVITY IN THE IRIS OF THE NEONATE. Lind, N., Shinebourne, E., Turner, P. and Cottom, D. (St. Bartholomew's Hospital, London, E.C. 1, England), Pediatrics 47:105-111, Jan., 1971.

In premature and full-term infants, the response of the dilator pupillae muscle to directly and indirectly acting sympathetic amines was measured. Phenylephrine always produced a mydriasis, whereas the response to tyramine and hydroxyamphetamine, which was positively correlated with age, tended to be absent in the least mature, smaller babies. The results indicate that, in this situation, the end organ has the capacity to respond to the sympathetic neurohumoral transmitter, but that the synthesis, storage, or release of neuronal noradrenaline may be deficient. (6 figures, 19 references)—Authors' abstract

## PLASTIC AND RECONSTRUCTIVE SURGERY

A FOLLOW-UP STUDY ON THE TREATMENT OF KELOIDS WITH TRIAMCINOLONE ACETONIDE. Griffith, B. H., Monroe, C. W. and McKinney, P. (Department of Surgery (Plastic) Northwestern University Medical School, Chicago, Illinois), Plast. Reconstr. Surg. 46:145-150, Aug., 1970.

An aqueous suspension of triamcinolone acetonide (Kenalog) was injected into 151 keloids and 12 hypertrophic scars and reduced the size of the lesion in over 9.0% of the cases. There was no recurrence of keloid formation in 10 patients after a keloid was excised and triamcinolone was injected into the wound edges.—Bartley R. Frueh

## TRANSACTIONS OF THE AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

DIABETES MELLITUS AND PRIMARY OPEN-ANGLE GLAUCOMA. Becker, B. (Washington University, St. Louis, Missouri), Tr. Am. Acad. Ophth. Otolaryng. 75:239-259, Mar.-Apr., 1971.

Primary open-angle glaucoma as well as elevated intraocular pressure, high intraocular pressure response to topical corticosteroids (gg), and C/D diameter ratios greater than 0.3 are more prevalent in diabetics than in nondiabetics. . . . Proliferative retinopathy occurs less often in diabetics with primary open-angle glaucoma, elevated intraocular pressure, gg response to topical corticosteroids, or high myopia.

Diabetes and positive glucose tolerance tests are more prevalent in patients with primary open-angle glaucoma and in high intraocular pressure responders to topical corticosteroids (gg). . . . Positive glucose tolerance tests are much more prevalent in the gg subgroup more "susceptible" to field loss (normal circadian variation and dexamethasone suppression of plasma cortisol, large C/D diameter ratio, and reversible changes in visual field induced by intraocular pressure elevation) than in "resistant" gg subgroup. . . . Positive glucose tolerance tests are more prevalent in glaucoma patients with lower intraocular pressures; glaucoma patients with positive test results appear to lose visual field at lower intraocular pressures and higher outflow facilities than do those with negative test results. (2 figures, 20 tables, 54 references)—Author's abstract

CATARACTS AND PRIMARY OPEN-ANGLE GLAUCOMA: THE EFFECT OF UNCOMPLICATED CATARACT EXTRACTION ON GLAUCOMA CONTROL. Bigger, J. F. and Becker, B. (Washington University, St. Louis, Missouri), Tr. Am. Acad. Ophth. Otolaryng. 75:260-272, Mar.-Apr., 1971.

The effects of uncomplicated, intracapsular cataract extraction on the control of intraocular pressure were determined in a study of 100 eyes with primary open-angle glaucoma . . . Of the eyes in which the glaucoma was well controlled prior to cataract extraction, 88% were either as well or better controlled one year later. For the eyes with marginal or poor control preoperatively, improvement was noted in 74% and 50%, respectively, one year later. Although all 100 eyes required medication before surgery, 20 eyes were adequately controlled without medication postoperatively. Only two eyes required subsequent glaucoma surgery during the first two years after cataract extraction. (9 tables, 12 references)—Authors' abstract

CATARACT EXTRACTION IN MANAGEMENT OF GLAUCOMA. Linn, Jr., J. G. (University of Pittsburgh School of Medicine), Tr. Am. Acad. Ophth. Otolaryng. 75:273-280, Mar.-Apr., 1971.

A review of 98 cataract operations performed on eyes under medical treatment for glaucoma was made to determine the influence of the operation on the control of the glaucoma. No medical treatment for glaucoma was required in 40 eyes. The medical control of the glaucoma after cataract surgery was approximately the same or better in 94 of the 98 eyes. The difficulty in preoperative medical control was not helpful in identifying those patients who would have a problem with glaucoma after cataract extraction. The experience with this group of patients would indicate that the cataract operation is usually an aid in the management of glaucoma and seldom makes control worse. (2 figures, 2 tables, 9 references)—Author's abstract

FAMILIAL AND SECONDARY DRUSEN: HISTOLOGIC AND FUNCTIONAL CORRELATIONS. Farkas, T. G., Krill, A. E., Sylvester, V. M. and Archer, D. (Eye Research Laboratories, University of Chicago, Ill.), Tr. Am. Acad. Ophth. Otolaryng. 75:333-343, Mar.-Apr., 1971.

One patient with familial drusen and another patient with acquired drusen were studied by histologic and functional methods. The patient with familial drusen was found to have abnormalities of retinal function and histologic evaluation revealed a diffuse disturbance of the pigment epithelium. The patient with acquired drusen had normal retinal function and only a focal abnormality of the pigment epithelium, based on histologic studies. The histochemical, light microscopic, and electron microscopic findings in the two types of drusen were identical. Drusen are the result of abnormal behavior of the pigment epithelium and

represent a common response of this structure to a variety of abnormal stimuli. (12 figures, 2 tables, 19 references)—Authors' abstract

TREATMENT OF PROLIFERATIVE SICKLE RETINOPATHY. Goldberg, M. F. (University of Illinois Eye and Ear Infirmary, Chicago), Tr. Am. Acad. Ophth. Otolaryng. 75:532-556, May-June, 1971.

Twenty-seven eyes with PSR were treated, primarily by xenon arc photocoagulation. The average follow-up duration was 30.4 months. The number of retinas with neovascularization was reduced from 100% to 55% and the number of eyes with vitreous hemorrhage was reduced from 41% to 26%. Of the total number of neovascular lesions, 74% were obliterated by photocoagulation. The reduction in extent of retinal neovascularization was statistically significant when compared with an untreated group control group of eyes. Intervention thus appeared to interrupt the natural course of PSR. (12 figures, 8 tables, 10 references)—Author's abstract

PHOTOCOAGULATION OF MACULAR LESIONS. Gass, J. D. (Bascom Palmer Eye Institute, University of Miami, Florida), Tr. Am. Acad. Ophth. Otolaryng. 75:580-608, May-June, 1971.

The author advises photocoagulation of idiopathic central serous choroidopathy if a leak can be demonstrated with fluorescein at least one-fourth disc diameter from the fovea. In general, one should wait four months to allow for spontaneous resolution. Patients with senile macular choroidal degeneration benefit from photocoagulation if there is no hemorrhagic component and if there is a serous detachment of the retina extending into the central macular area. Hemangiomas of the choroid respond very well to photocoagulation and one should particularly treat those lesions that are associated with serous detachments of the macula. Only moderate photocoagulation of the tumor surface is required, and no attempt should be made to destroy the benign tumor with additional photocoagulation. (13 figures, 1 table, 27 references)—David Shoch

ARGON AND RUBY LASER PHOTOCOAGULATION OF DISCIFORM MACULAR DISEASE. L'Esperance, Jr., F. A. (Edward S. Harkness Eye Institute, New York), Tr. Am. Acad. Ophth. Otolaryng. 75:609-625, May-June, 1971.

The use of either the ruby or the argon laser may be beneficial in patients with disciform macular disease. Success rate is 93% in those with central serous choroidopathy and falls to 27% in those with hemorrhagic detachment of the neuroepithelium. In most of these cases there is no return of central vision but the progression of the disciform maculopathy is stopped. (13 figures, 1 table, 15 references)—David Shoch

LASER INTERFEROMETRY IN THE EVALUATION OF POTENTIAL MACULAR FUNCTION IN THE PRESENCE OF OPACITIES IN THE OCULAR MEDIA. Green, D. G. and Cohen, M. M. (University of Michigan, Ann Arbor), Tr. Am. Acad. Ophth. Otolaryng. 75:629-637, May-June, 1971.

A subjective test for evaluating retinal function in patients with moderate to dense cataractous changes is described. This test uses coherent light from a low-output, helium-neon laser to form striped interference frings on the retina. The patient's ability to see interference fringes of varying fineness provides a basis for estimating potential visual acuity through opacities in the ocular media.

The validity of the test has been assessed by comparing estimated visual potential with the actual visual acuity present after cataract surgery. The correlation between preoperatively predicted visual acuity and best corrected aphakic vision is high enough to suggest that this test is a useful addition to present methods of preoperatively determining macular function. (5 figures, 7 references)—Authors' abstract

PHOTOCOAGULATION OF IRIS-CILIARY BODY EPITHELIAL CYSTS. Cleasby, G. W. (Presbyterian Hospital of Pacific Medical Center, San Francisco), Tr. Am. Acad. Ophth. Otolaryng. 75:638-642, May-June, 1971.

Many types of treatment and surgical procedures have been advocated for elimination of iris-ciliary body epithelial cysts. All of these methods carry certain hazards and photocoagulation is at least as effective and is much safer than any of the techniques used in the past. (9 figures, 11 references)—Author's abstract

# NEWS ITEMS

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For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### ULTRASONICS: WORLD CONGRESS IN ROTTERDAM

The second world congress on ultrasonics in medicine will be held June 4–8, 1973, in "de Doelen" Congress Center in Rotterdam under the Chairmanship of the Dutch neurologist, M. de Vlieger, M.D. This congress on medical diagnostics with the aid of ultrasound is held under the auspices of the medical faculty at Rotterdam and the World Federation for Ultrasound in Medicine and Biology.

For further information, contact the secretariat of the Second World Congress on Ultrasonics in Medicine, Holland Organizing Center, 16 Lange Voorhout, The Hague, Netherlands.

### VISUAL SCIENCE INFORMATION CENTER

The Visual Science Information Center, a computer-based bibliographic information center covering the world's literature on vision, has been established at the University of California, Berkeley. Its bibliographic information services are available to the public.

The data base begins with publications released after November, 1970. Some entries before that date are included, but no comprehensive coverage is intended. An index of authors and subjects, Vision Index, will be issued quarterly, with each quarterly issue containing an annual accumulation expected to be approximately 2500 individual entries. Annual subscription price in the United States, Canada, and Mexico is $20; in other countries it is $21. Volume 1, number 1 (March, 1971) is now available.

For subscription to Vision Index, demand search request forms, and further information write Harold R. Gibson, Director, Visual Science Information Center, University of California, Berkeley, California 94720.

### AMERICAN BOARD OF OPHTHALMOLOGY EXAMINATIONS

The written qualifying test of the American Board of Ophthalmology is held annually on the third Monday in January in approximately 35 locations throughout the world. Applications to take this test in any one year must be in the Board's office, postmarked not later than July first of the preceding year.

The dates for the forthcoming oral examinations are as follows: Thursday, October 21 thru Sunday, October 24, 1971, at the Sheraton Hotel in Chicago; Thursday, May 18 thru Sunday, May 21, 1972, at the Sheraton-Palace Hotel in San Francisco; and Thursday May 17 thru Sunday, May 20, 1973, at the Sheraton Hotel in Boston.

For further information contact the American Board of Ophthalmology, 8870 Towanda Street, Philadelphia, Pennsylvania 19118.

### PROJECT VISION EXPANDED: INTERNATIONAL EYE FOUNDATION

John Harry King, founder and medical director of the International Eye Foundation, announced that Project Vision, supported through private donations and funding granted by the USAID, has been expanded to include the countries of Ethiopia, Kenya, and Saudi Arabia. A teaching team headed by Dr. King visited these countries during the month of August, while at the same time, Dr. A. Benedict Rizutti, New York, heads a team of surgeons flown to Saudi Arabia under the auspices of the Foundation. Project Vision, sponsored by the IEF, is a continuous program to upgrade world eye care, and to help in the prevention and cure of blindness. At the request of the host countries, the IEF teaching teams will help set up an eye bank program and programs to teach the latest eye surgery techniques.

### POSTGRADUATE CONFERENCE: ESTELLE DOHENY EYE FOUNDATION

The Estelle Doheny Eye Foundation will sponsor its third annual postgraduate conference at the Ambassador Hotel in Los Angeles, Monday and Tuesday, October 18 and 19.

The A. Ray Irvine and Wendell C. Irvine Memorial Lecturers will be Ramon Castroviejo, Professor of Clinical Ophthalmology, City University of New York Postgraduate School of Medicine, and Frank W. Newell, Professor and Chairman, Department of Ophthalmology, University of Chicago School of Medicine.

Registration information may be obtained by writing to Robert E. Levine, M.D., or T. Rodman Wood, M.D., Program Chairmen, Estelle Doheny Eye Foundation, 272 South Lake Street, Los Angeles.

### MICROSURGERY COURSE: DOWNSTATE UNIVERSITY OF NEW YORK

The State University of New York Downstate Medical Center will hold an intensive course in microsurgery of the eye, March 25–28, 1972. Speakers will include Richard C. Troutman, Professor of Ophthalmology, State University of New York, Gunter Mackensen, Freiburg, Germany, and Enrique S. Malbran, Buenos Aires, Argentina, together with the members of the ophthalmology staff of the medical center.

Registration will be limited to 22 students. Each

student will be provided with a zoom surgical microscope. Instruction will be carried out by films, closed-circuit television and by lectures. The course will be directed to the practical application of microscope magnification in surgery of the anterior segment, with particular emphasis on cataract surgery and surgery of the cornea, but including aspects of surgery for glaucoma, the uveal tract, and trauma.

Further information is available from Mrs. Sylvia Baer, Division of Ophthalmology, State University of New York, 450 Clarkson Avenue, Brooklyn, New York 11203.

### Conference on Craniofacial Anomalies: New York University Medical Center

An international conference on the diagnosis and treatment of craniofacial anomalies will be held at the New York University Medical Center October 25–28, 1971, under the joint-chairmanship of a physician, John Marquis Converse, and a dentist, Samuel Pruzansky. The subjects covered will be a classification of the various syndromes including a review of the embryology and development of the craniofacial area, premature craniofacial synostosis, otocephalic syndromes and maxillomandibular disharmonies. Registration fee is $200 ($50 for residents in training).

### Wills Eye Hospital: Annual clinical conference

The 24th annual clinical conference of the Wills Eye Hospital will be held at the Bellevue Stratford Hotel, Philadelphia, February 3–5, 1972. Lorenz E. Zimmerman of Washington, D.C., will deliver the Bedell lecture. Robert D. Mulberger is chairman of the conference committee.

### Postgraduate courses: Mount Sinai School of Medicine

The Mount Sinai School of Medicine of the City University of New York and the Page and William Black Postgraduate School of Medicine will offer the following postgraduate courses for ophthalmologists during the 1971–72 academic year: Edward L. Raab will offer an introduction to strabismus. On Tuesdays, January 13 and 20, from 3:00 to 5:00 P.M. Heskel M. Haddad will instruct in a course on metabolic and pediatric ophthalmology, to be held February 7 through 28 from 8:00 to 10:00 A.M. A course in accommodative and non-accommodative esodeviations will be instructed by Edward L. Raab on Thursdays, February 10, 17, and 24, from 3:00 to 5:00 P.M.

The fee for each of the first two courses is $40. The fee for the last course is $60. For a descriptive catalogue and an application, write to the registrar, Page and William Black Postgraduate School of Medicine, Fifth Avenue and 100th Street, New York, New York 10029.

### New Jersey Academy of Ophthalmology and Otolaryngology

The New Jersey Academy of Ophthalmology and Otolaryngology will hold its annual meeting at the Robert Treat Hotel in Newark November 10, 1971.

The program for ophthalmologists is as follows: Treatment of corneal ulcers and burns will be presented by Stuart Brown, New York; advances in retinal detachments will be the subject of MacKenzie Freeman, Boston; photocoagulation therapy will be discussed by Harold F. Spalter, New York; etiology, diagnosis, and results of treatment of superior oblique palsy will be presented by Donelson R. Manley, Philadelphia; cryosurgical method for the treatment of retinal detachment will be discussed by Harvey Lincoff, New York; A-V patterns is the subject of Webb Chamberlain, Cleveland; some complications in cataracts surgery will be described by Samuel D. McPherson, Durham, North Carolina; and management of bacterial corneal ulcers will be discussed by Frederick H. Theodore, New York.

### Alumni meeting: Washington Hospital Center

The annual meeting of alumni of the Department of Ophthalmology of the Washington Hospital Center, Washington, D.C., will be held June 3, 1972.

For further information contact Seymour Dubroff, M.D., Chairman, 1111 Spring Street, Silver Spring, Maryland 20910.

### Soft lens course: University of Florida

A practical course on soft contact lenses sponsored by the University of Florida will be held January 26–29, 1972, in Gainesville. The course is designed to provide instruction in the selection, fitting, and uses of all types of soft contact lenses. The faculty includes: J. Aquavella, J. Baldone, C. Black, V. Chiquiar Arias, G. Feldman, M. Friedberg, A. Gasset, J. Hartsein, H. Kaufman, M. Poster, W. Sampson, M. Uotila, and K. Whitman.

Registration fee will be $100 for the seminar and $300 for the seminar and workshop. Deadline for applications is December 1, 1971. For information contact Antonio R. Gasset, M.D., Department of Ophthalmology, University of Florida College of Medicine, Gainesville, Florida 32601.

## Personals

### Jorge Vasco Posada

Jorge Vasco Posada, auxiliary professor of ophthalmology at the Medical College of the University of Antioquia, Medellin, Colombia, was awarded the 1971 silver medal, Ignacio Barraquer y Barraquer, by the Honor Tribunal of the National Academy of Medicine. The ceremony took place in Bogota. Dr. Vasco Posada received this award for his outstanding achievements in the field of ophthalmology, and especially for his work in the modification of circulation of the posterior segment of the eye.

### George N. Schoonover

On September 30, George N. Schoonover, Chairman and Chief Executive Officer of the House of Vision, Inc., resigned from the company. H. Clinton Green, who has been president of House of Vision since 1968, was elected to the additional post of Chief Executive Officer.

# The American Society of Contemporary Ophthalmology



## ANNUAL MEETING

**DIPLOMAT**
**HOTEL**
**HOLLYWOOD, FLORIDA**

**February 27-March 3, 1972**

MONDAY 9:00 A.M.

February 28

**Cancer Symposium**

George Moore, M.D.
Chairman
Harvey Lincoff, M.D.
Bernard Fisher, M.D.
Frederic Mohs, M.D.
Setrag Zacarian, M.D.
Andrew Gage, M.D.

QUESTIONS & ANSWERS

2:00 P.M. to 5:00 P.M.

**Genetics, Uveitis, and Squint**

Jules Francois, M.D.
Chairman
Yi-Yung Hsia, M.D.
Theo. Schlaegel, M.D.
Edward Dunlap, M.D.

**ENTERTAINMENT FOR WIVES AND CHILDREN**
**Golf, Tennis and Swimming**

TUESDAY 9:00 A.M.

February 29

**Cataract Symposium**

Harold Scheie, M.D.
Chairman
Robert Schimek, M.D.
Norman Jaffe, M.D.
Miles Galin, M.D.
Ralph Kirsch, M.D.
John Bellows, M.D.

2:00 P.M. to 5:00 P.M.

**Glaucoma and Lid Surgery**

Saul Sugar, M.D.
Chairman
Miles Galin, M.D.
Sidney Fox, M.D.
Crowell Beard, M.D.

WEDNESDAY 9:00 A.M.

March 1

**Rentina Symposium**

Charles Schepens, M.D.
Chairman
Graham Dobbie, M.D.
Michael Shea, M.D.
Harvey Lincoff, M.D.
Kenneth Hovland, M.D.
C. Hilsdorf, M.D.

New Concepts in Pathogenesis
Medical Therapy, Surgery

*Individual Conferences with experts highlight meeting.*

**PRACTICAL COURSES**

WEDNESDAY and THURSDAY

2:00 P.M. to 5:00 P.M.

Jose Barraquer, M.D.
Chairman
Microscopic Surgery of the Cornea

Charles Schepens, M.D.
Chairman
Binocular Ophthalmoscopy

LIMITED ENROLLMENT

ADDITIONAL FEE FOR EACH COURSE $50.00

THURSDAY 9:00 A.M.

March 2

**Corneal Symposium**

Herbert Kaufman, M.D.
Chairman
David Donaldson, M.D.
Stuart Brown, M.D.
Donald Willard, M.D.
Drs. Jose & Francisco Barraquer

FRIDAY 9:00 A.M.

March 3

**Ocular Infections**

James H. Allen, M.D.
Chairman
James H. Allen, M.D.
Henry F. Allen, M.D.
Herbert Kaufman, M.D.
Roderick MacDonald
Melvin Rubin, M.D.

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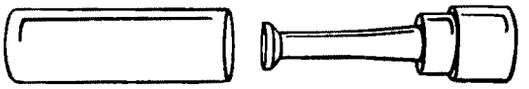
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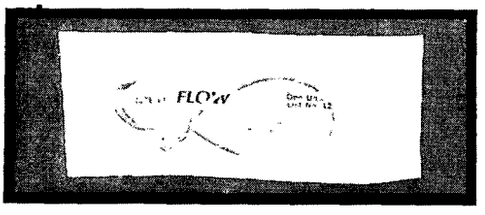
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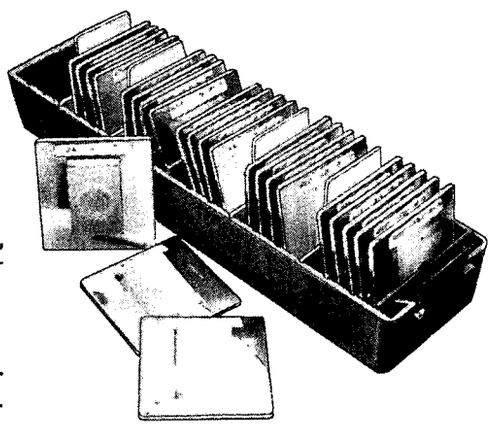
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*JAMA 214:5 (Nov. 2, 1970), 835-6

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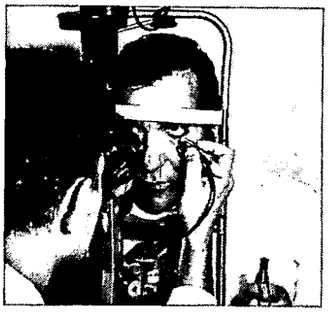
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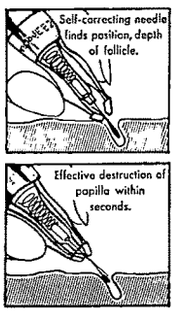
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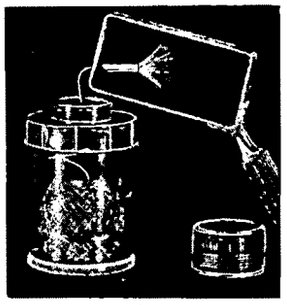
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# Title 21—FOOD AND DRUGS

## Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER A—GENERAL

(Abstract)

## PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

### Use of Impact-Resistant Lenses in Eyeglasses and Sunglasses

In the FEDERAL REGISTER of October 2, 1970 (35 F.R. 15402), a notice was published in which the Commissioner of Food and Drugs proposed that Part 3 be amended by adding a statement of general policy regarding the use of impact-resistant lenses in eyeglasses and sunglasses. The notice provided for the filing of comments within 30 days, and this time period was extended to January 30, 1971, by a document published in the FEDERAL REGISTER of November 3, 1970 (35 F.R. 16937). An announcement was published in the FEDERAL REGISTER of November 6, 1970 (35 F.R. 17116), advising interested parties that the effective date of the proposal when adopted would be December 31, 1971. . . . . .

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(j), 701(a), 52 Stat. 1051, 1055; 21 U.S.C. 352(j), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Part 3 is amended by adding thereto the following new section:

§3.84 Use of impact-resistant lenses in eyeglasses and sunglasses.

(a) Examination of data available on the frequency of eye injuries resulting from the shattering of ordinary crown glass lenses indicate that the use of such lenses constitutes an avoidable hazard to the eye of the wearer.

(b) The consensus of the ophthalmic community is that the number of eye injuries would be substantially reduced by the use in eyeglasses and sunglasses of either plastic lenses, heat-treated crown glass lenses, or lenses made impact-resistant by other methods.

(c) To protect the public more adequately from potential eye injury, eyeglasses and sunglasses must be fitted with impact-resistant lenses, except in those cases where the physician or optometrist finds that such lenses will not fulfill the visual requirements of the particular patient, directs in writing the use of other lenses, and gives written notification thereof to the patient.

(d) The physician or optometrist shall have the option of ordering heat-treated glass lenses, plastic lenses, laminated glass lenses, or glass lenses made impact resistant by other methods; however, all such lenses must be capable of withstanding an impact test in which a 5/8-inch steel ball weighing approximately 0.56 ounce is dropped from a height of 50 inches upon the horizontal upper surface of the lens. The ball shall strike within a 5/8-inch diameter circle located at the geometric center of the lens. The ball may be guided, but not restricted, in its fall by being dropped through a tube extending to within approximately 4 inches of the lens. In order to pass the test, the lens must not fracture (for the purpose of this section, a lens will be considered to have fractured if it cracks through its entire thickness and across a complete diameter into two or more separate pieces or if any lens material visible to the naked eye becomes detached from the ocular surface). The test shall be conducted with the lens supported by a tube (1-inch inside diameter, 1¼-inch outside diameter, and approximately 1-inch high) affixed to a rigid iron or steel base plate. The tube shall be made of rigid acrylic plastic, steel, or other suitable substance and shall have on the top edge a 1/8- by 1/8-inch neoprene gasket having a hardness of 40±5, as determined by ASTM Method D 1415; a minimum tensile strength of 1,200 pounds, as determined by ASTM Method D 412; and a minimum ultimate elongation of 400 percent, as determined by ASTM Method D 412. The diameter and/or contour of the lens support may be modified as necessary so that the 1/8- by 1/8-inch neoprene gasket supports the lens at its periphery. Each finished impact-resistant glass lens (including each impact-resistant laminated glass lens) for prescription use shall be subjected to the impact test prescribed by this paragraph. To demonstrate that all other types of impact-resistant lenses are capable of withstanding this impact test, the manufacturer of such lenses shall subject to the impact test a statistically significant sampling of lenses from each production batch, and the lenses so tested shall be representative of the finished forms as worn by the wearer (including finished forms that are of minimal lens thickness and that have been subjected to any treatment used to impart impact resistance). This statement of policy will be appropriately amended to provide for use of alternate methods of testing the impact resistance of lenses if it can be shown that the alternate method is equal to or superior to the method prescribed in this paragraph.

(e) In addition to the invoice(s) and shipping document(s), all packages and/or shipping containers of impact-resistant lenses, other than impact-resistant glass lenses (including impact-resistant laminated glass lenses) for prescription use, shall bear a code or mark in a form or manner that will permit future identification of any given production batch by the manufacturer.

(f) The manufacturer of the lenses shall make, keep, and maintain for 3 years records of sale, distribution, and the results of tests conducted in accordance with paragraph (d) of this section. The manufacturer shall make such records available upon request at all reasonable hours by any officer or employee of the Food and Drug Administration or by any other officer or employee acting on behalf of the Secretary of Health, Education, and Welfare and shall permit such officer or employee to inspect and copy such records, to make such inventories of stock as he deems necessary, and otherwise to check the correctness of such inventories.

(g) For the purposes of this section, the term "manufacturer" includes an importer for resale. Such importer may have the tests required by paragaph (d) of this section conducted in the county of origin; however, such importer of impact-resistant lenses is subject to and must comply with the records and inspections provisions of paragraph (f) of this section.

(h) The transition to impact-resistant lenses must start immediately and be completed as promptly as possible; however, to provide for the development of an adequate supply of impact-resistant lenses and to facilitate an orderly change over to these lenses, the effective date of this statement of policy will be December 31, 1971. After that date eyeglasses and sunglasses must be fitted with impact-resistant lenses, except when the physician or optometrist finds that impact-resistant lenses will not fulfill the visual requirements of a particular patient.

(i) This statement of policy does not apply to contact lenses.

(Secs. 502(j), 701(a), 52 Stat. 1051, 1055; 21 U.S.C. 352(j), 371(a)) . . . . . .

[FR Doc. 71-6802 Filed 5-14-71; 8:47 am]




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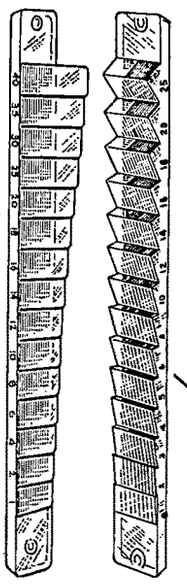
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| Jorge N. Buxton, M.D. | New York City, N.Y. |
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1. Mishima, S. and D. M. Maurice, The Effect of Normal Evaporation on the Eye, Exp. Eye Res., 1:46, 1961.
2. Bahr, Gunnar, Measurement of the Effect of Solutions of Different Osmotic Pressure on the Thickness of the Living Cornea, Trans. of Ophthal. Soc. U.K., 68:515, 1949.

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| Dr. Claes Dohlman | Dr. Gordon Miller |
| Dr. Max Fine | Dr. Edward W. D. Norton |
| Dr. Richard Forster | Dr. Frank Polack |
| Dr. J. Donald M. Gass | Dr. Marvin Quickert |
| Dr. Russell Harner | Dr. Norman Sanders |
| Dr. Danny Jones | Dr. Byron Smith |
| Dr. A. Dalma Kende | Dr. David Soll |

Dr. Richard Tenzel

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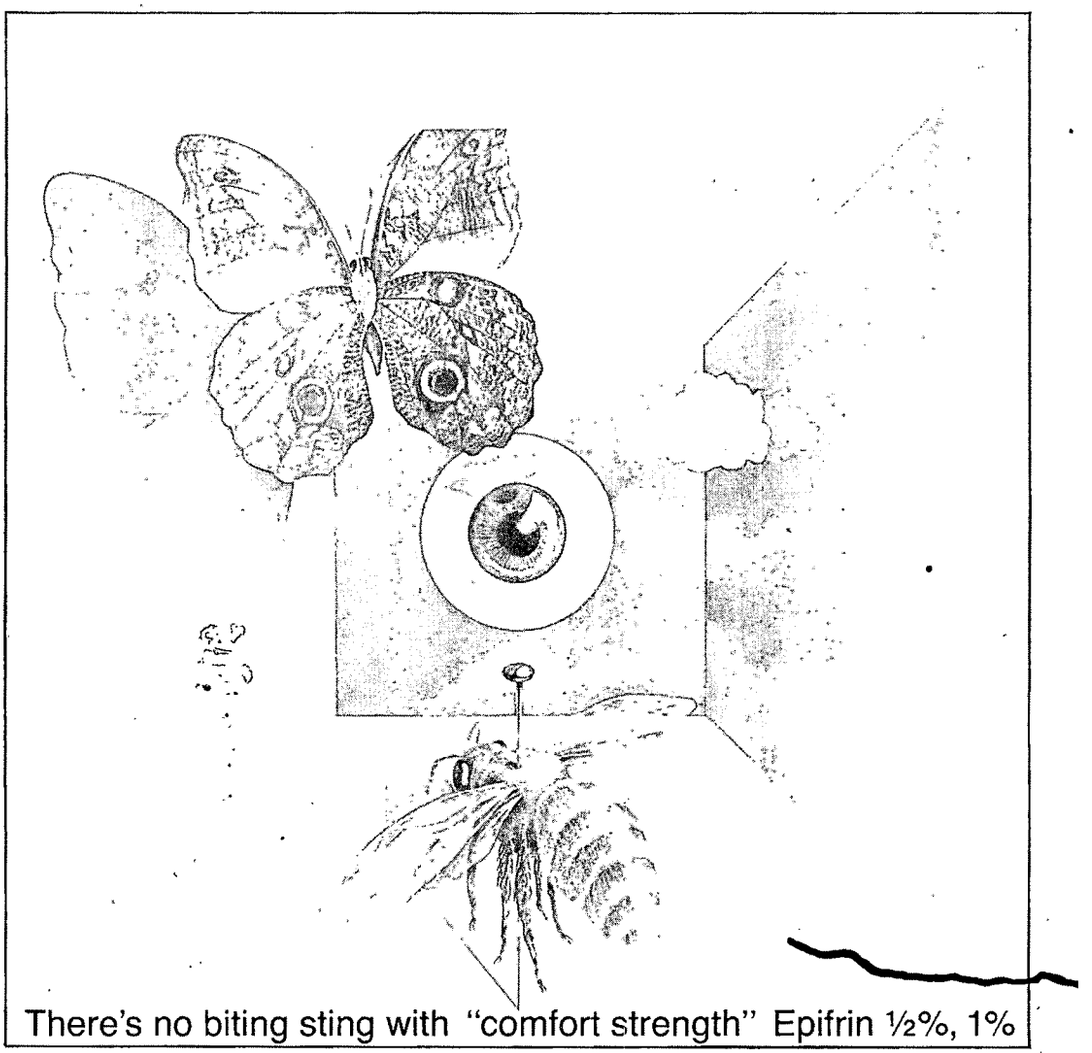

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VOLUME 72 NUMBER 5 NOVEMBER, 1971

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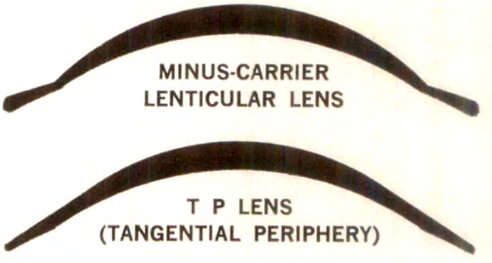
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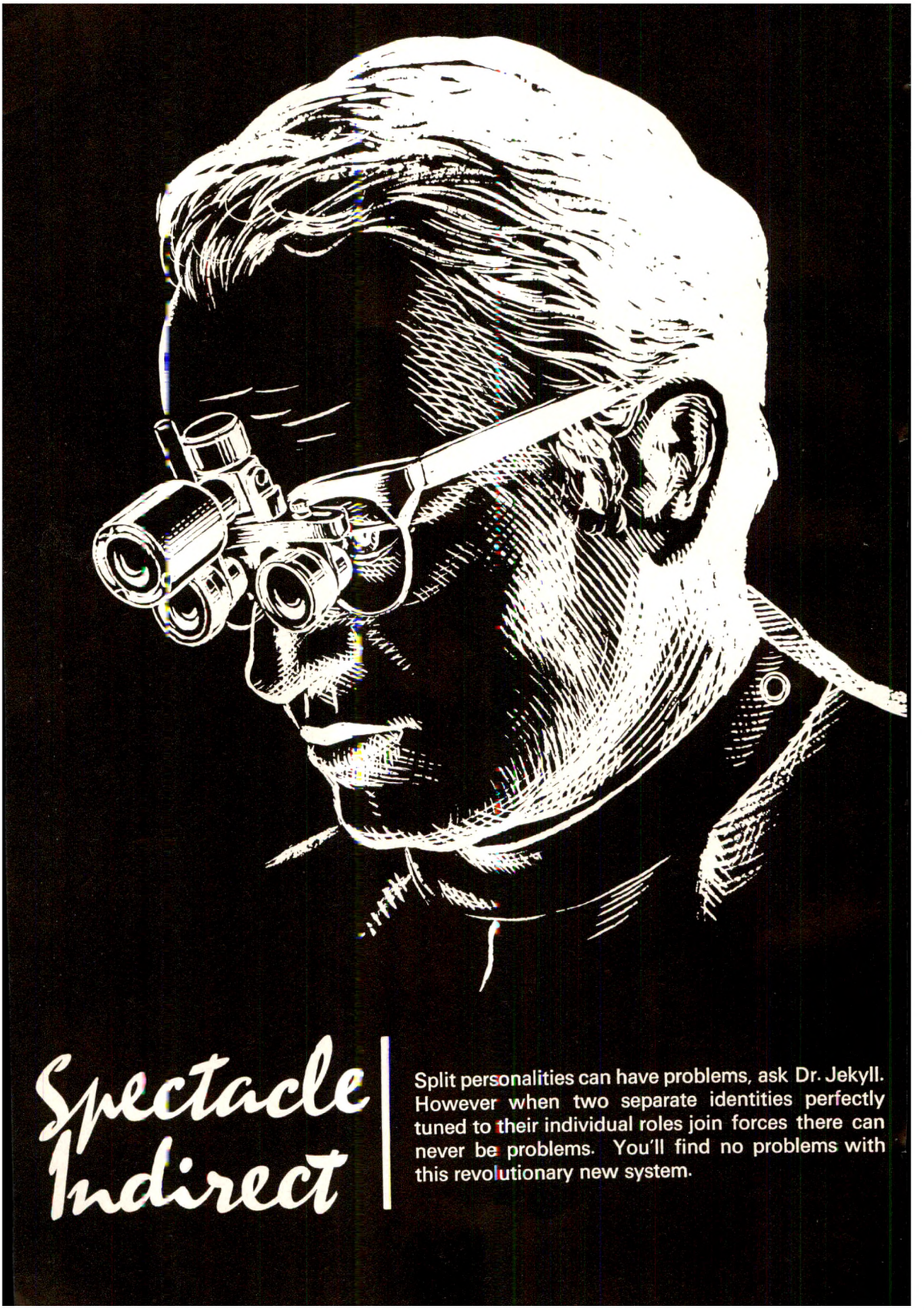
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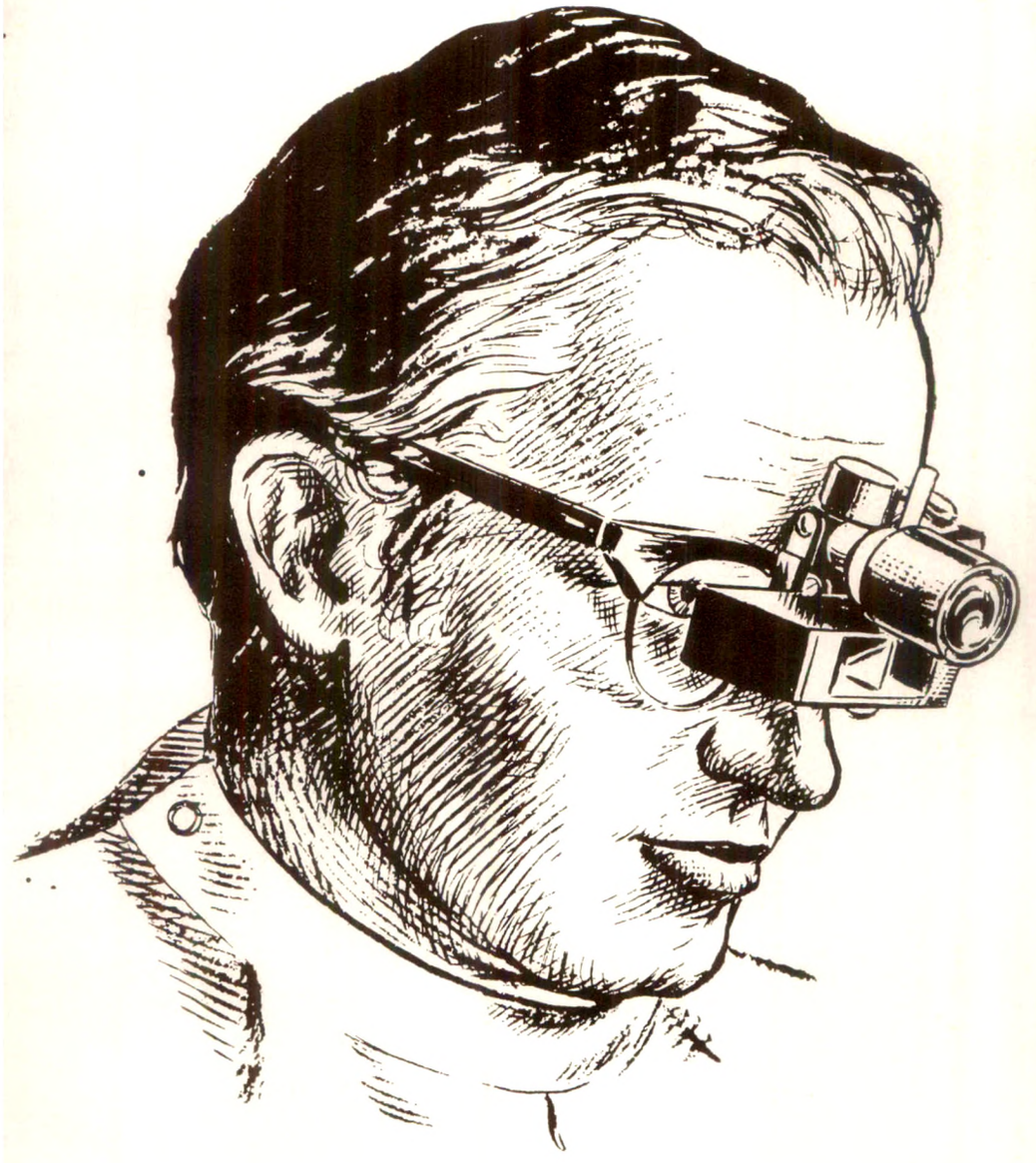





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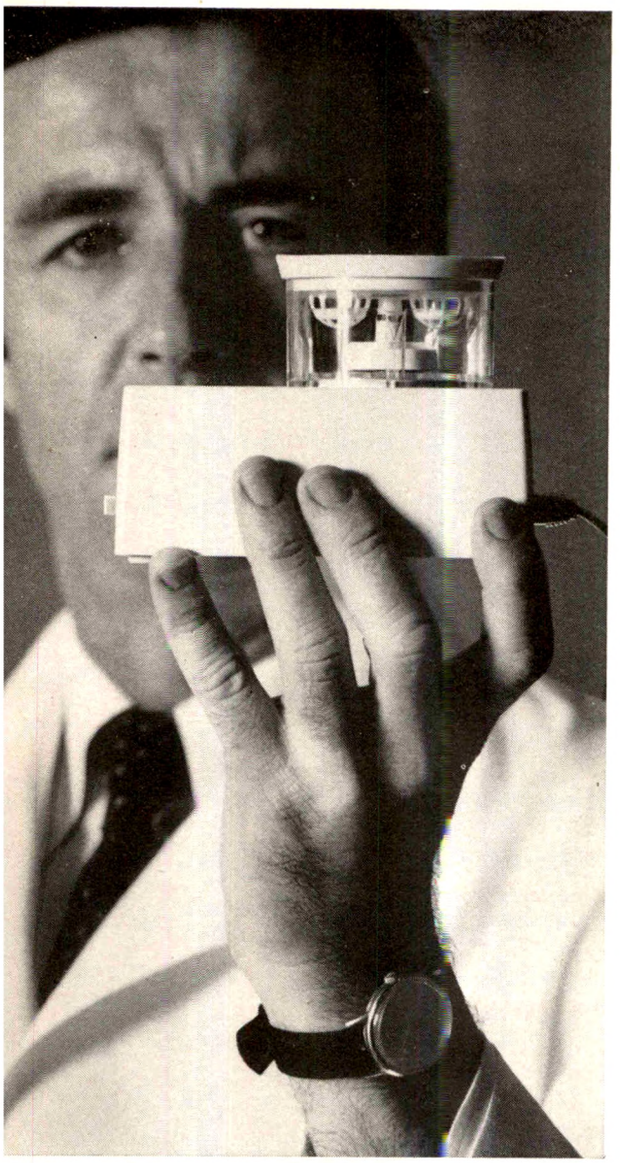
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Until now, the most common method cleaning contact lenses has been to rub the between the fingers. As you know, this syste has three serious drawbacks: 1) it doesn't clea properly; 2) it *can* scratch or warp lenses; 3) may not be sanitary.

### A new, more efficient technique

The new Swirl Clean electric contact le cleaner by Contique approaches the problem a totally different manner: It combines th cleaning power of a high-speed agitator wi the detergent action of Contique Cleaning Sol tion. The result is thorough but gentle clea ing—with a minimum of handling and le chance of lens loss.

Swirl Clean doesn't stop there. It provid a convenient place to soak and store lenses b tween wearings.

### Perfect for office use

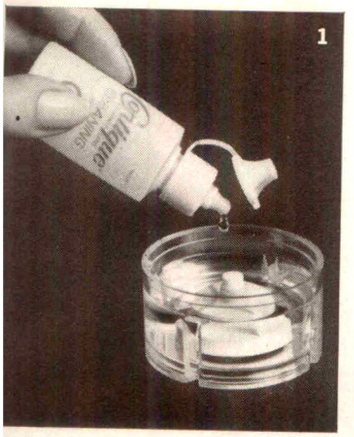
How many times have you wished for ju such an efficient way to clean your patien contacts—when you are delivering a new pa or after making an adjustment?

Swirl Clean fills this long-felt need pe fectly. It's compact. Easy to use. And it *loo* highly professional. Your patients can s you've gone to the expense of securing the mo advanced cleaning device available to mal sure their lenses are clean and comfortable.

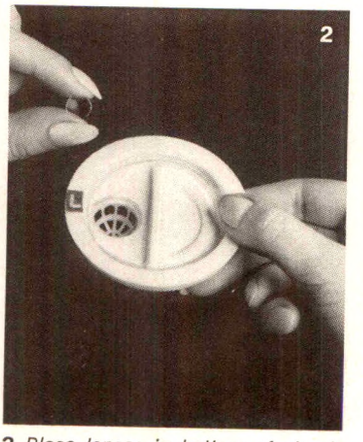
And it takes only a few seconds to clea contacts with the Swirl Clean. Once you get in the habit, you'll wonder how you managed wit out it.

### Your patients will want one, too

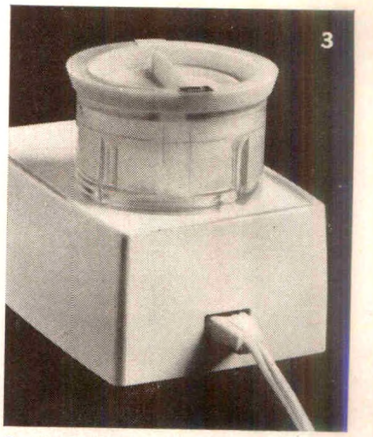
When they see how effortlessly you clea their contacts with the Swirl Clean, your ne contact lens wearers will want one of their ow to use at home. That's why it makes good bus ness sense to stock a few units to sell or recor mend to your patients. They'll never be mo psychologically receptive than at the mome




1 *Fill cleaning chamber ¾ full with cold water. Add 6-8 drops of Contique Cleaning Solution and place on base.*




2 *Place lenses in bottom of clearly marked LEFT and RIGHT baskets of lens holder. Close lid. Place lens holder on cleaning chamber.*




3 *Flip "ON" switch and run Swirl Clean 30-60 seconds. You can see the lenses being swirled clean before your eyes.*

hey get their new contacts. It's also a good way of starting them off on a proper lens-care regimen and helping them become satisfied wearers.

### Read what Swirl Clean users say

An O.D. in Knoxville, Tenn. writes: "The compactness of this unit makes its use a pleasure in my office." An M.D. in Bakersfield, Calif. calls Swirl Clean "a very valuable asset to our office." An optician in Long Beach, Calif.: "Excellent method of cleaning lenses after lab adjustment."

Enthusiastic comments have also come in from contact lens wearers all over the country. "My vision is so much better with clean contacts." (Boston, Pa.) "I enjoy its convenience and notice my lenses are more comfortable." (East Point, Ga.) "Cleans lenses 100% better than by hand." (Hyde Park, Mass.) "I wear lenses 16 hours a day and find their comfort greatly increased." (Indianapolis, Ind.)

These comments are on file at Alcon Laboratories and may be examined by anyone interested.




### Complete lens care by Contique

Used with the new Swirl Clean, *Contique Cleaning Solution* dissolves eye-irritating deposits such as mucus, oil and film. Yet it's so gentle you can recommend it with complete confidence. *Contique Soaking Solution* "conditions" lenses by keeping them chemically moist when stored in the special Swirl Clean soaking dish, increasing wettability and wearing comfort. *Contique Wetting Solution* creates a liquid cushion between lens and eyes, makes placement smooth and easy, and can also be used to re-wet lenses during the day.

This family of lens care products from Contique can help your patients become successful, satisfied contact lens wearers. Almost $6 worth of Contique solutions are packed with every Swirl Clean at no additional cost. For more information about the new Swirl Clean and other Contique products, call your optical wholesaler today.

OPTICAL PRODUCTS DIVISION, ALCON LABORATORIES, INC., P.O. BOX 1959, FORT WORTH, TEXAS 76101

**Indications:** Relief and management of nonpurulent Blepharitis and Conjunctivitis.

**Dosage:** Initially, 1 or 2 drops placed in the conjunctival sac every hour until improvement occurs.

Thereafter, 1 or 2 drops 2 to 4 times daily.

**Composition:**

Prednisolone-21-phosphate sodium .....0.25%
(Equivalent to Prednisolone 0.2%)
Sulfacetamide sodium ....10.0%
Phenylephrine HCl .....0.125%
Methylparaben .....0.02%
Propylparaben .....0.005%

In a stabilized aqueous solution containing sodium thiosulfate and *SMP-68 (a combination of polyoxypropylene compound and polysorbate 80).

**Effectiveness:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**Caution:** Federal law prohibits dispensing without prescription.

**Contraindications:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**Supplied:** Plastic dropper-tipped vials, 5 cc.

**Smith, Miller & Patch, Inc.**
401 Joyce Kilmer Avenue
New Brunswick. N.J. 08902

It's a lousy feeling
to wake up in the morning
with your eyelids
stuck together.



No medication residue with Vasocidin.
Nothing to wash away in the morning.
It's an antibacterial, steroid, decongestant combination in true solution.
Works fast because it disperses fast.
Helps relieve nonpurulent blepharitis and conjunctivitis more effectively.
Starts the day right.

# Vasocidin

a clear solution that isn't sticky

# The crystal drop assures stability




As you may be aware, the first sign of deterioration in a product containing epinephrine is a color change . . . reddish-brown or "yellowing." Each clear drop of PE* Ophthalmics is its own proof of stability . . . as also evidenced in clinical studies involving unrefrigerated shelf life, temperature changes and exposed-to-air studies simulating patient use. Proven shelf life, over 3 years (for maximum assurance, vials are date-coded on a 2 year basis). No change in clarity or potency was evidenced in any tests. The crystal clarity of every drop assures your patient full therapeutic effect, first drop to last.

PE* Ophthalmics provide simple *one-solution* treatment of open angle glaucoma . . . eliminating patient error, assuring the physician exact evaluation of therapy. Available in 5* strengths, in 15cc color-coded vials, nationwide and in Canada.

*Pilocarpine Hydrochloride 1%, 2%, 3%, 4%, 6% with Epinephrine Bitartrate 1% (½% Epinephrine Base).

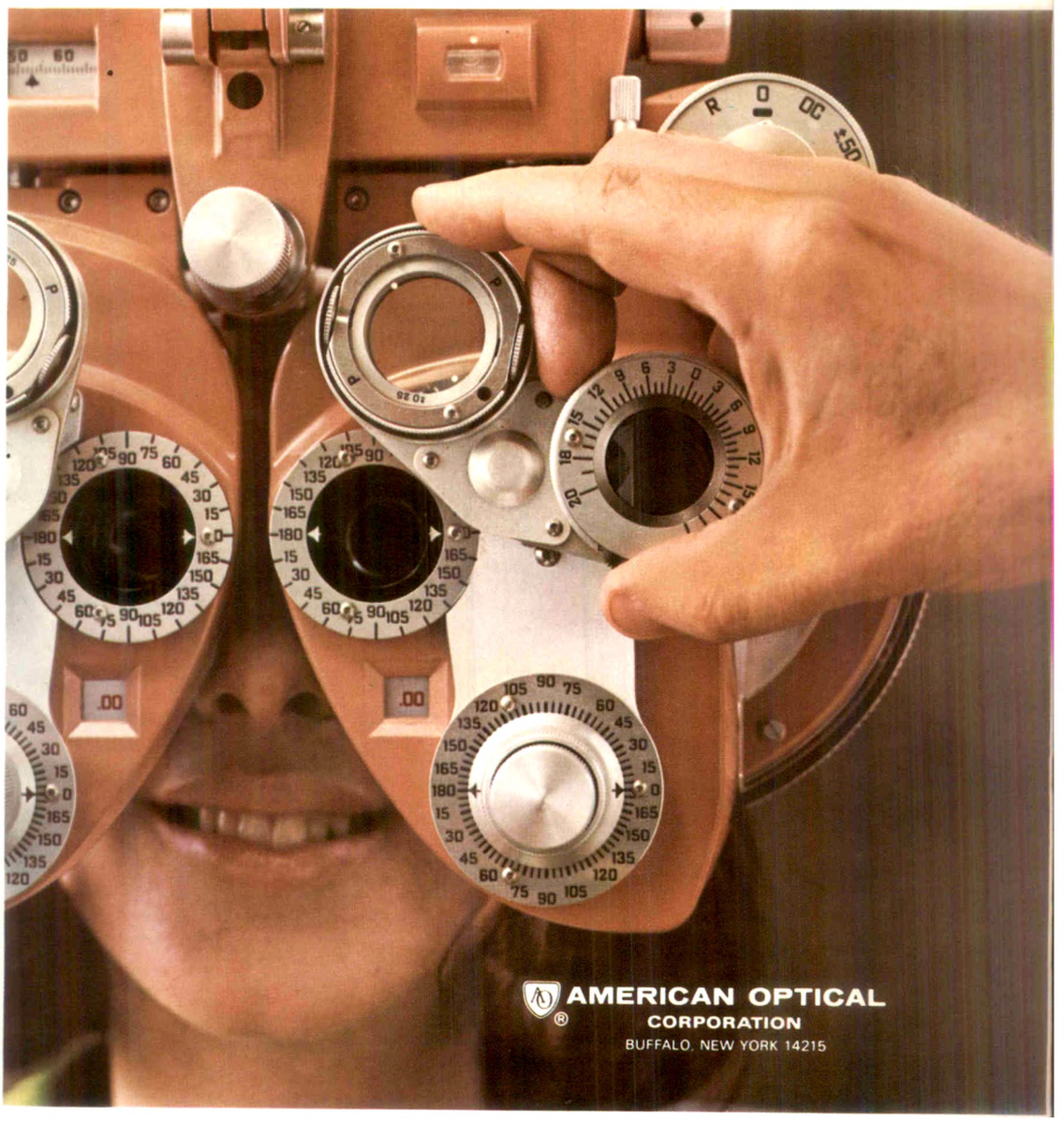
**Contraindication:** Narrow angle glaucoma. **Precautions:** Use with caution in unverified glaucoma and hypertension. If irritation or sensitization occurs, discontinuance may be necessary.

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# With the AO Ultramatic Phoroptor you take one reading, once, with one scale.

With the AO Ultramatic Phoroptor, you save time and simplify refracting technique every time you turn the dial. The secret: synchronization. The Cross Cylinder Loupe is synchronized so that it rotates automatically to a corresponding axis—every time you change the correcting cylinder axis. This feature alone eliminates numerous cross cylinder axis settings, saves valuable time. And when the axis check test is completed you make only one reading, once. The AO Ultramatic Phoroptor makes refraction easier for you—through synchronization.

*Turn the page for more.*



# A converging lens system is also exclusive with the AO Ultramatic Phoroptor.

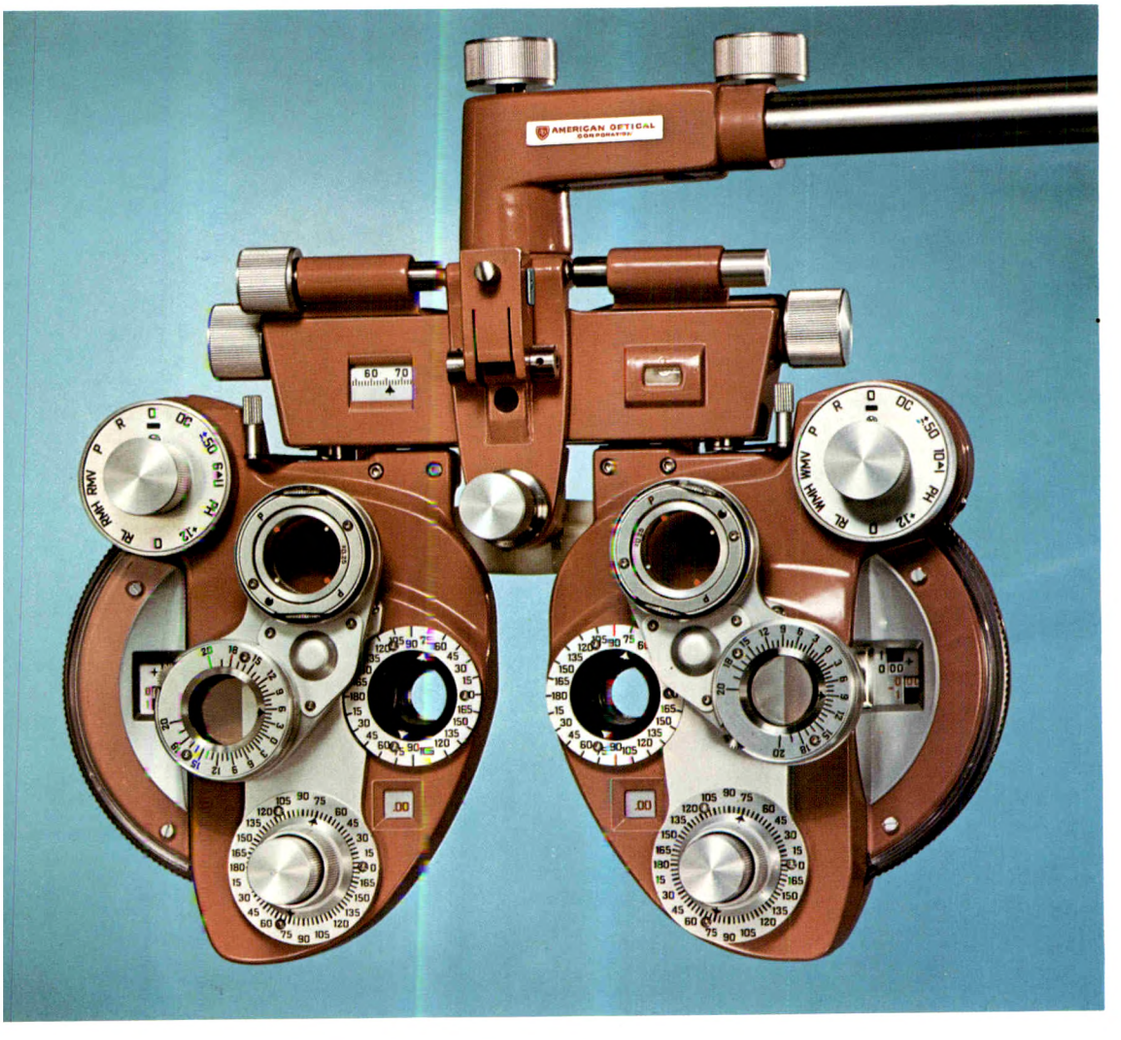
One of the major features of the Ultramatic Phoroptor is its exclusive Ful-Vue convergence lens system, for precision measurement in near as well as distance testing. This Ful-Vue convergence is easy to operate and provides the ideal near-test conditions for your patients. The patient looks through the optical centers of the instrument lenses, insuring overlapping fields and the widest field of view. In addition, ten most-used auxiliary lenses (plus 2 open apertures) in each side offer an unmatched choice to facilitate comprehensive testing in the shortest time.

High-contrast scales are another time-saving convenience. Large and easy to read, they're legible even in soft illumination.

Ask your AO Representative for more information about the AO Ultramatic Phoroptor.

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**Our researchers are still creating more firsts for your contact lens patients.**




**CLENS™** *The first cleaning solution* specifically designed for use by the patient. Rinses rapidly from the lens, removing films and deposits by its thorough cleansing action.

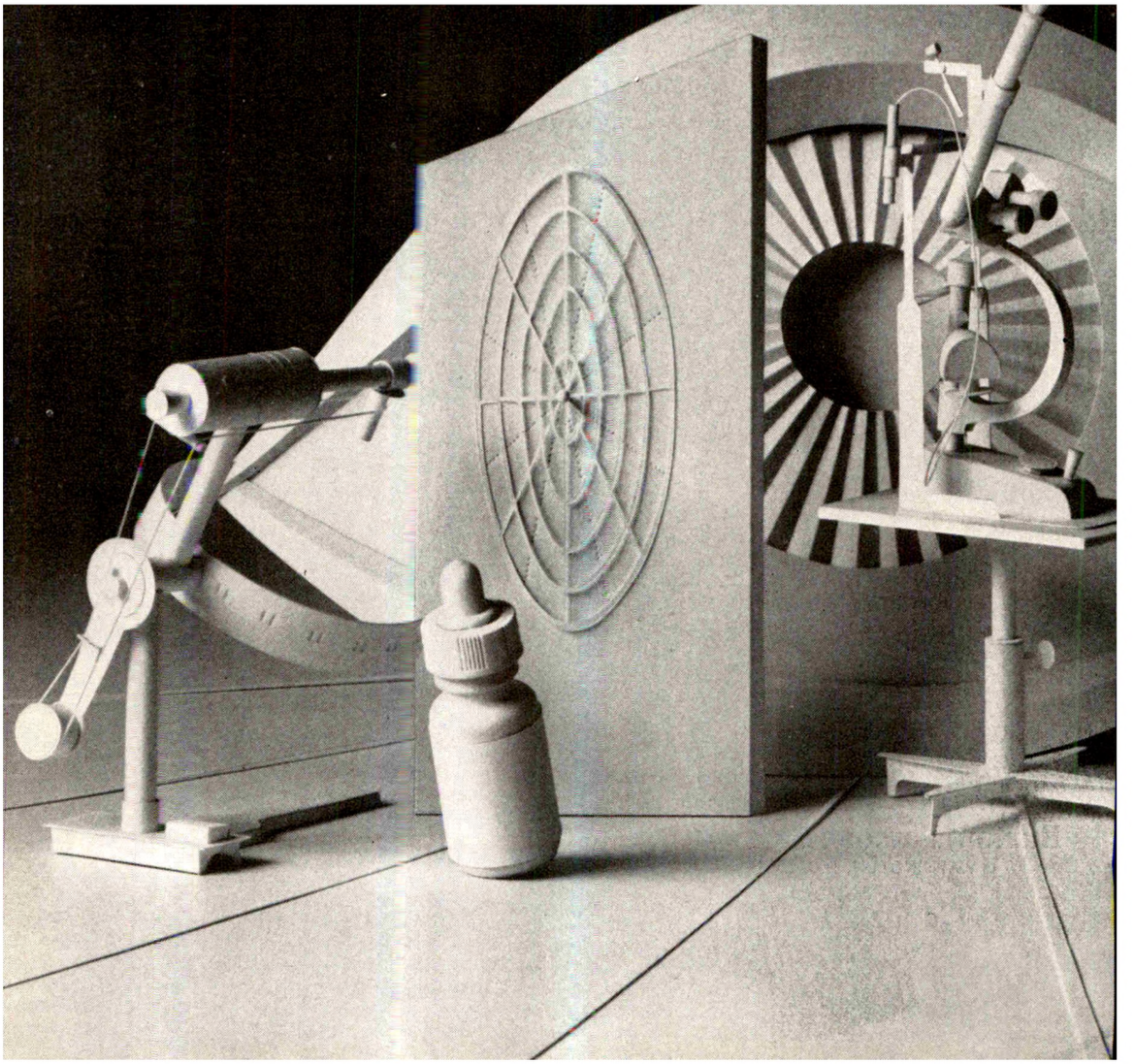
**SOACLENS™** *The first combination soaking-wetting solution* adjusted to the proper pH, eliminates necessity for application of separate wetting solution, and allows insertion of lens directly from a Soaclens bath.

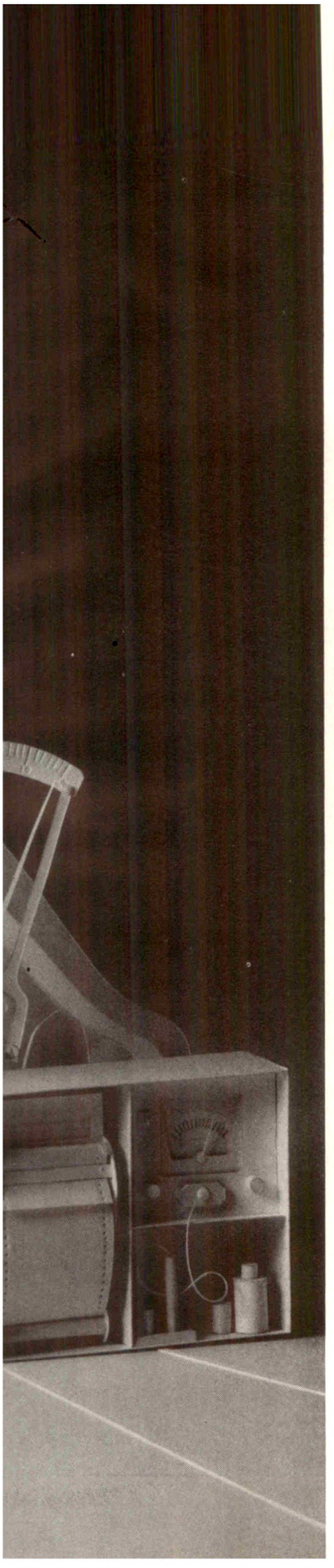
**ADAPT™** *The first cushioning solution.* Effectively reduces lens sensation and over-awareness. Ideal during adaptation and for chronic problem cases. Helpful, too, in providing extra comfort for well-adapted wearers.

*Write for literature and clinical samples:*

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# When epinephrine is indicated for the management of chronic simple (open-angle) glaucoma

# Ayerst Epitrate® BRAND OF epinephrine bitartrate

BRIEF SUMMARY

*(For full prescribing information, see package circular.)*

**Epitrate®** (epinephrine bitartrate)

***For management of chronic simple (open-angle) glaucoma***

**Description:** A sterile aqueous solution of levorotatory epinephrine bitartrate 2% (equivalent to 1.1% base), it is stable, retains its potency throughout use, and requires no refrigeration. It has a low surface tension.

**Action:** Intraocular pressure is lowered by reducing the rate of aqueous formation. Improvement in outflow facility is also observed in certain cases following prolonged therapy.

**Indications:** Useful in management of chronic simple (open-angle) glaucoma, either alone or in combination with miotics. In selected cases, it may also be used with carbonic anhydrase inhibitors.

**Contraindications:** Prior to peripheral iridectomy, an epinephrine preparation is contraindicated in eyes that are capable of angle closure since its relatively weak mydriatic action may, nevertheless, precipitate angle block. Gonioscopy should be carried out on all patients before initiating therapy.

**Warnings:** Topical use of epinephrine in any form should be interrupted prior to general anesthesia with certain anesthetics such as cyclopropane or halothane which sensitize the myocardium to sympathomimetics.

**Precautions:** EPITRATE (epinephrine bitartrate) should be used with caution in the presence of hypertension, diabetes, hyperthyroidism, heart disease, and cerebral arteriosclerosis because of the possibility of systemic action.

**Adverse Reactions:** As with other epinephrine solutions, transitory stinging on initial instillation may be expected. Headache or browache frequently occur on beginning EPITRATE therapy, but usually diminish as treatment is continued. Conjunctival allergy occurs occasionally. Pigmentary deposits in the lids, conjunctiva or cornea may occur after prolonged use of epinephrine eyedrops. In rare cases, maculopathy with a central scotoma may result from the use of topical epinephrine in aphakic patients; prompt reversal generally follows discontinuance of the drug. Systemic effects have occasionally been reported, such as: palpitation, tachycardia, extrasystoles, hypertension, trembling, sweating, and pallor.

**Dosage and Administration:** 1 drop, with frequency of instillation being individualized, from every two or three days to twice daily. More frequent instillation than one drop four times daily does not usually elicit any further improvement in therapeutic response.

**How Supplied:** No. 1015—EPITRATE—ophthalmic solution of epinephrine bitartrate 2% (equivalent to 1.1% base). [Also contains chlorobutanol (chloral derivative) 0.5%, methylaminoaceto pyrocatechol HCl, sodium bisulfite, sodium chloride, polyoxypropylene-polyoxyethylene-diol, and disodium edetate.] Package containing 7.5 cc. bottle with separate dropper-screw cap attachment.

The Ophthalmos Division
**AYERST LABORATORIES**
New York, N.Y. 10017

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This Journal publishes original articles on every aspect of the ophthalmological sciences by practising ophthalmologists and research workers all over the world. While welcoming reports on experimental work, the editors nevertheless pay special attention to the practical problems of eye disorders and their treatment, to give as much help as possible to ophthalmic surgeons and all concerned with clinical ophthalmology. All articles are in English and carry summaries wherever appropriate.
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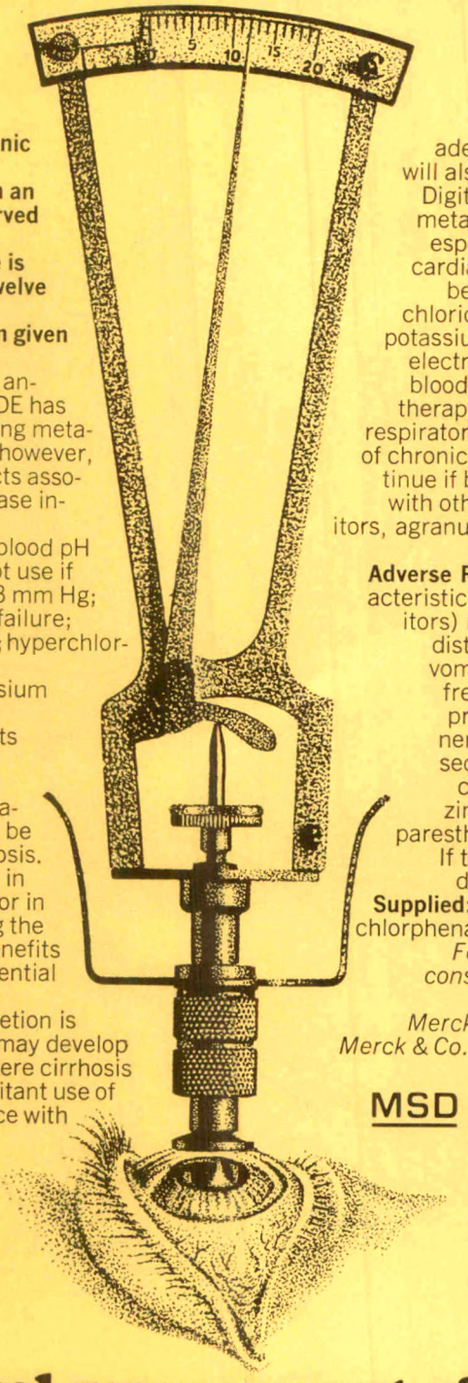
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# the measure of success...



- **orally effective, potent carbonic anhydrase inhibitor**
- **onset of action usually within an hour; maximal effect is observed in two to four hours**
- **lowered intraocular pressure is often maintained for six to twelve hours**
- **usually most successful when given in conjunction with miotics**

Compared to other carbonic anhydrase inhibitors, DARANIDE has a lesser propensity for causing metabolic acidosis. Please note, however, that this and other side effects associated with carbonic anhydrase inhibitors may occur.

**Contraindications:** To avoid blood pH decreases below 7.20, do not use if arterial $pCO_2$ greater than 63 mm Hg; hepatic insufficiency; renal failure; adrenocortical insufficiency; hyperchloremic acidosis; conditions in which sodium and/or potassium serum levels are depressed. Should not be used in patients with severe pulmonary obstruction who are unable to increase their alveolar ventilation since their acidosis may be increased to the point of narcosis.

**Warning:** Should not be used in women of child-bearing age or in pregnancy, especially during the first trimester, unless the benefits to be expected outweigh potential adverse effects.

**Precautions:** Potassium excretion is increased and hypokalemia may develop with brisk diuresis, when severe cirrhosis is present, or during concomitant use of steroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Hypokalemia may be treated by use of potassium chloride or giving foods with a high potassium content. A close check on electrolyte balance, blood pH, and blood gases should be kept during therapy. Use with caution in severe respiratory acidosis or in the presence of chronic pulmonary infection; discontinue if blood pH falls below 7.20. As with other carbonic anhydrase inhibitors, agranulocytosis, thrombocytopenia, or renal calculi are possible.

**Adverse Reactions:** Side effects (characteristic of carbonic anhydrase inhibitors) may include gastrointestinal disturbances (anorexia, nausea, vomiting), constipation, urinary frequency, mild skin eruptions, pruritus, headache, weakness, nervousness, globus hystericus, sedation, lassitude, depression, confusion, disorientation, dizziness, ataxia, tremor, tinnitus, paresthesias of hands, feet, tongue. If they occur, reduce dosage or discontinue drug temporarily.

**Supplied:** Tablets containing 50 mg dichlorphenamide each, in bottles of 100.

*For more detailed information, consult your MSD representative or see the Direction Circular.*

*Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

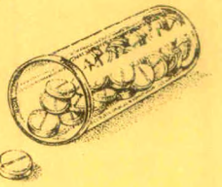
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## ...in the oral management of glaucoma

# DARANIDE®

## [DICHLORPHENAMIDE | MSD]

TABLETS, 50 mg





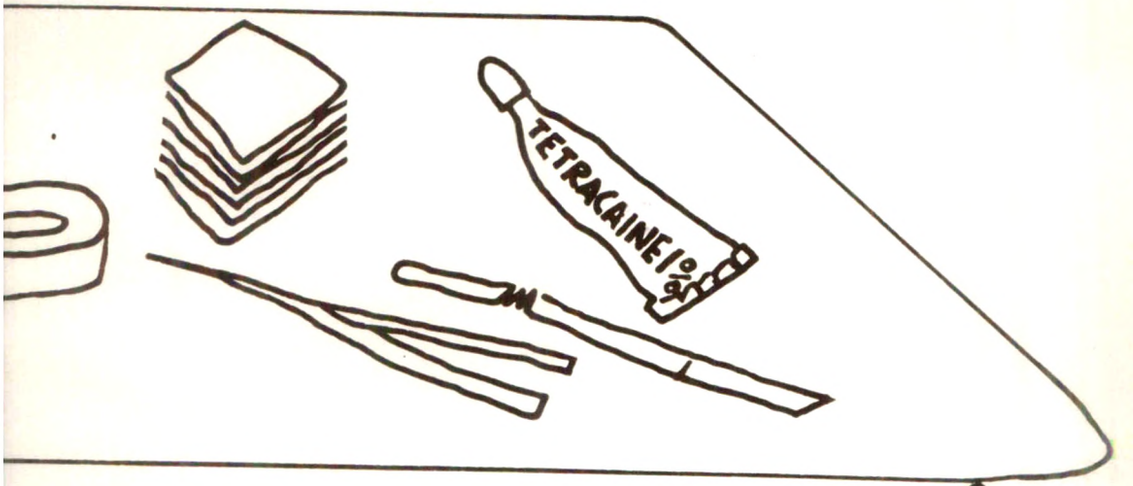
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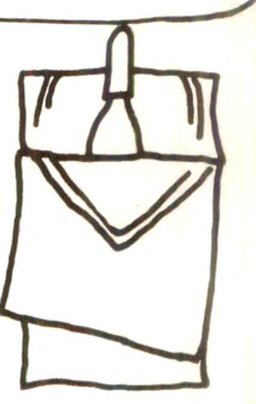
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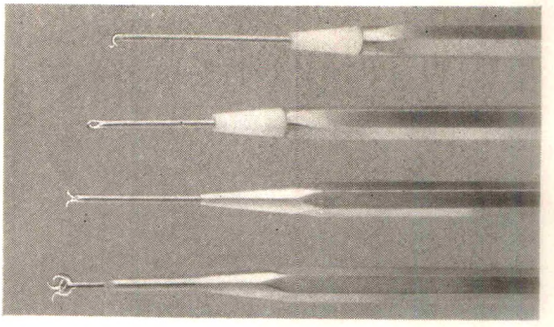
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### TWISTGRIPS

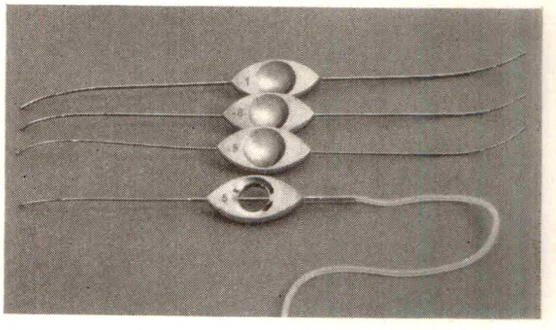
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☐ #MW84 Twistgrip @ $25 ☐ #MW84A Insulated Twistgrip, straight @ $30
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Reduces conjunctival hyperemia in minor eye irritation and ocular allergies. Helps after contact lens insertion and removal. Vasocon-A. Keeps them on the trail.

CAUTION: Federal law prohibits dispensing without prescription. See package insert before prescribing.

COMPOSITION: Naphazoline HCl, 0.05%; antazoline phosphate, 0.5%; boric acid, 1.2%; sodium carbonate anhydrous; sodium chloride; phenylmercuric acetate (preservative) 0.002%.

SIDE EFFECTS: Except for transitory stinging, side effects have rarely been encountered.

CONTRAINDICATIONS: Should not be used by patients with narrow angle glaucoma. If irritation persists or increases, patient should be advised to discontinue use and return to physician.

SUPPLIED: 15 cc plastic dropper-tip vials.

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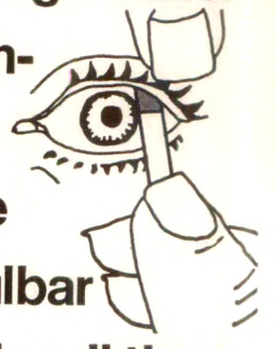
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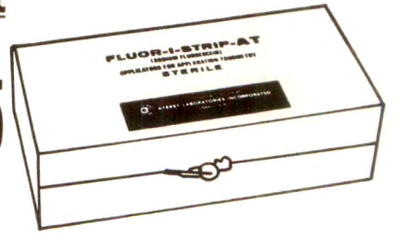


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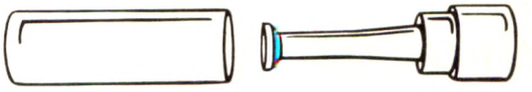

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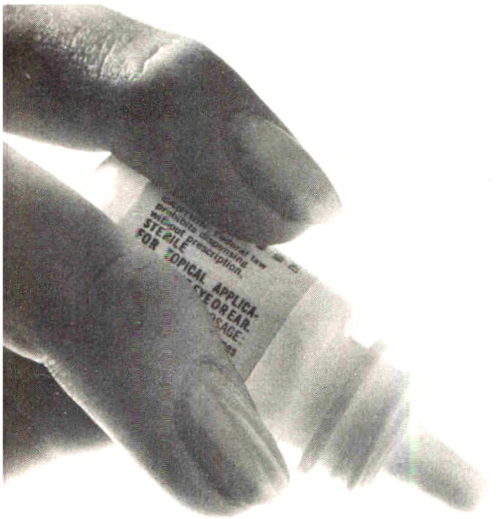
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esions of the eye, chickenpox,
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ometimes mask, activate, or
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/henever possibility of infection
xists, suitable antibiotic agents
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e considered. If infections do not
espond promptly, therapy should
e discontinued until the infection
as been adequately controlled
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ystemic side effects may occur
/ith extensive use of steroids.
'arely, ocular herpes simplex has
een reported in patients
eceiving adrenocortical steroids
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or other conditions.

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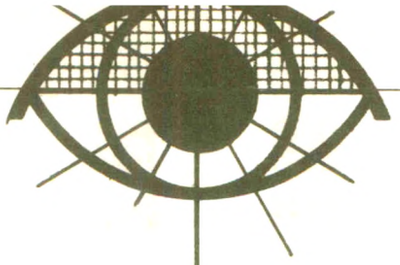
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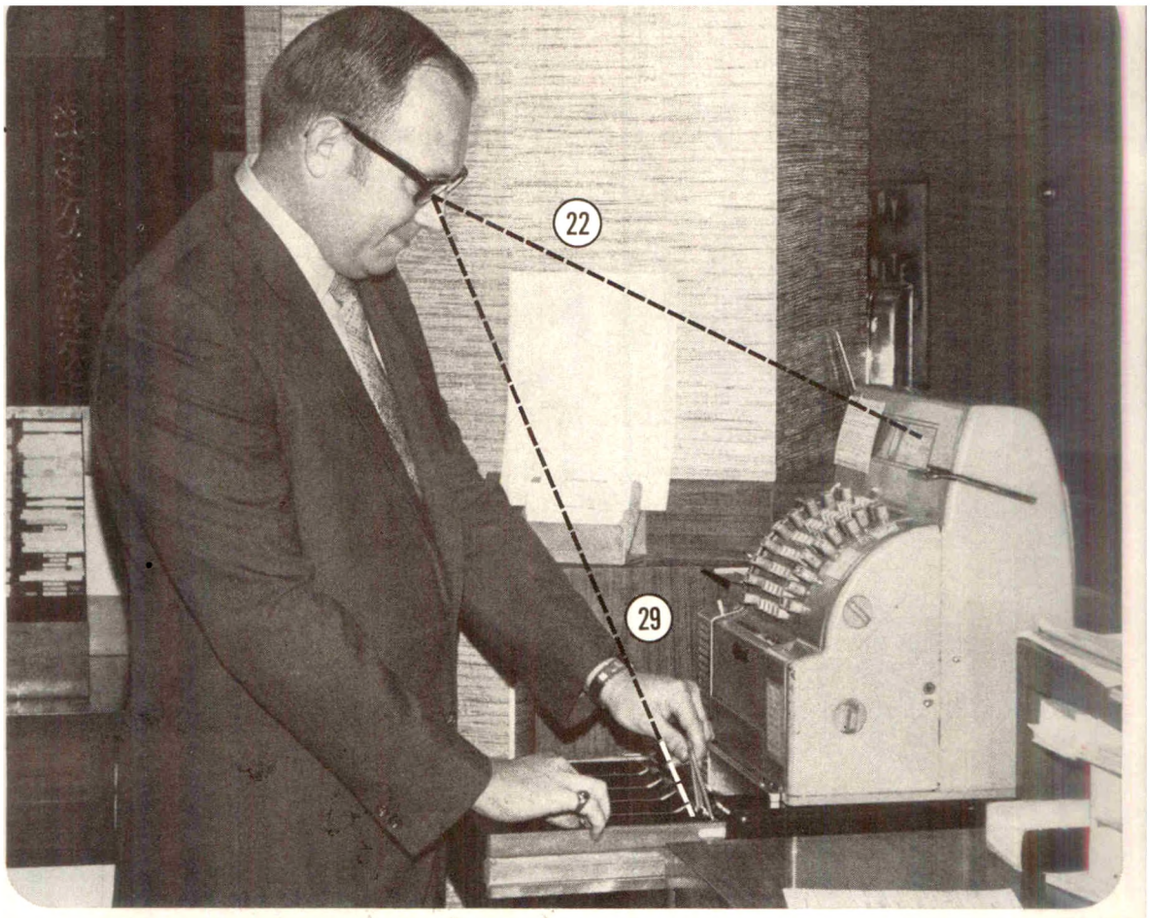
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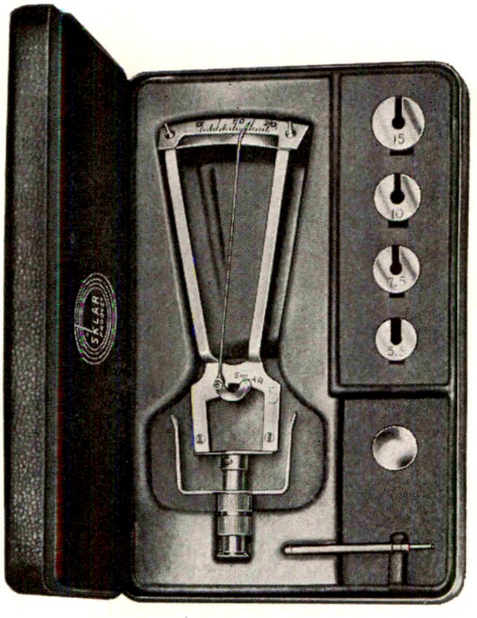
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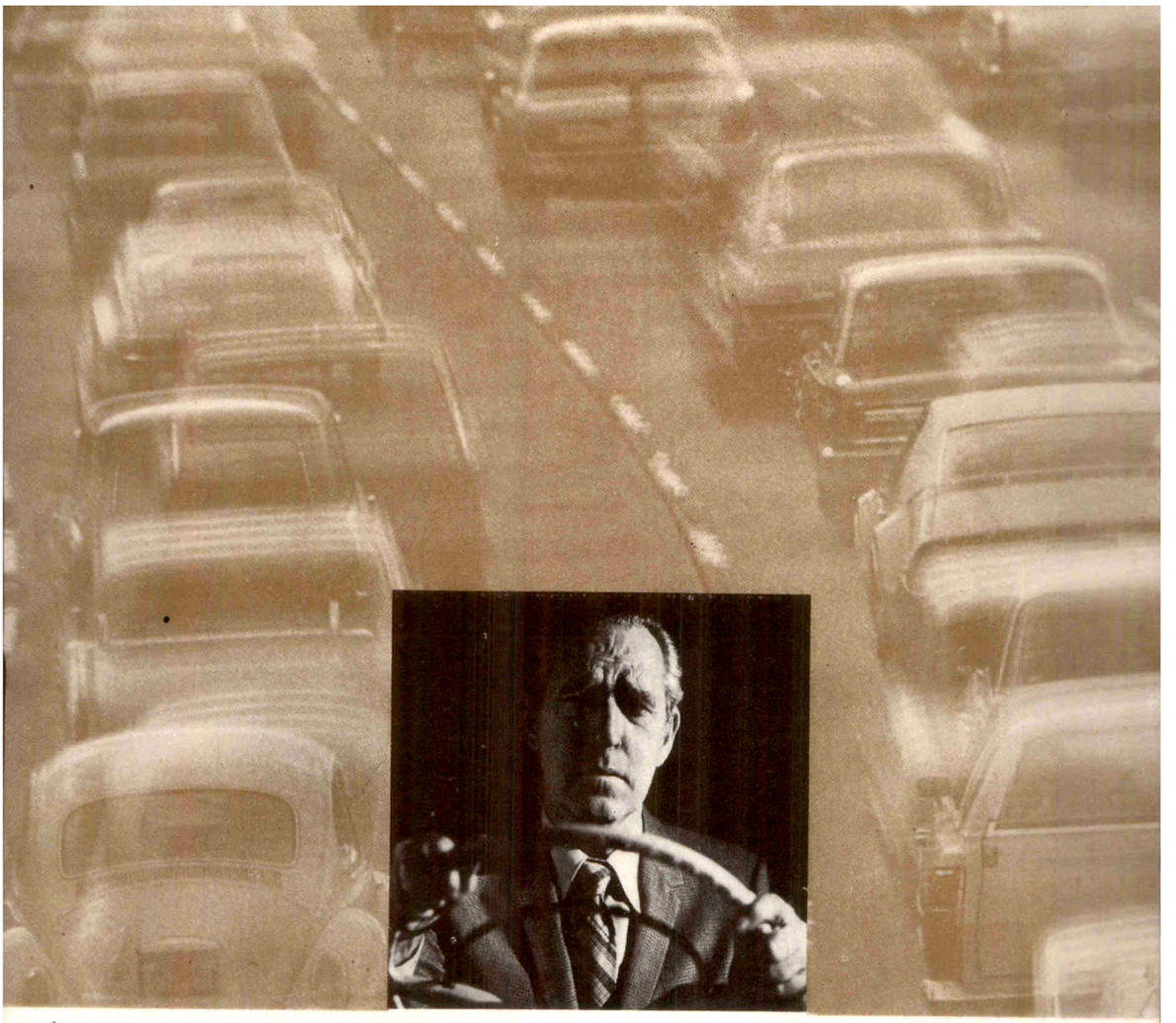
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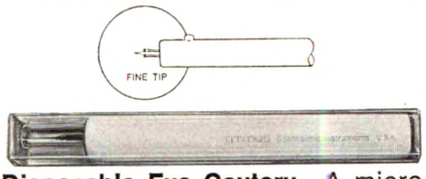
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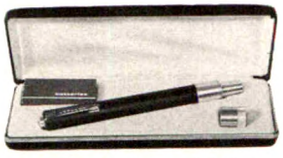
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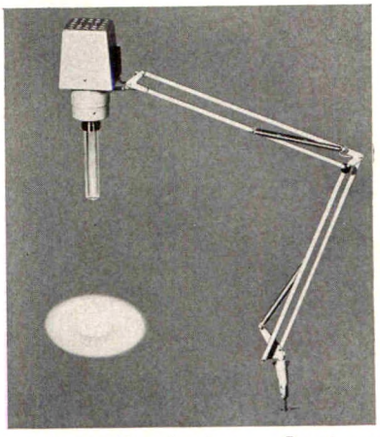

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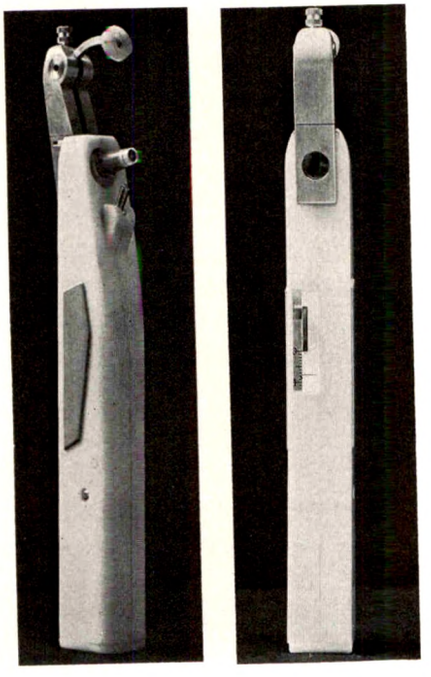


## ORA SERRATA ATTACHMENT TO THE GOLDMANN 3 MIRROR LENS

The periphery of the fundus near the ora serrata and the ciliary body cannot be examined under normal conditions with the 3-mirror lens alone. The ora serrata attachment along with the 3-mirror lens allows the observation of these most peripheral parts in its entire circumference.

The attachment is shaped like the 3-mirror lens. Half a steel-ball is fixed to the scleral part of the attachment which presses on the sclera above the ora serrata so that the fundus at its periphery near the ora serrata can be seen in the gonio mirror of the 3-mirror lens. The ora attachment can be used either with the 3-mirror lens in a locked or moveable position.

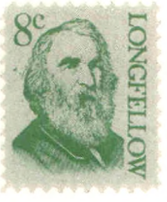
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**A NEW PRODUCT:** Implants—Sleeves (Tubes) for preventing adhesions in Eye Muscle Surgery. Method development by Edward A. Dunlap, M.D. Reference: Dunlap, Edward A.: Plastic Implants in Muscle Surgery, Archives of Ophthalmology, 80: 249-257, August 1968.

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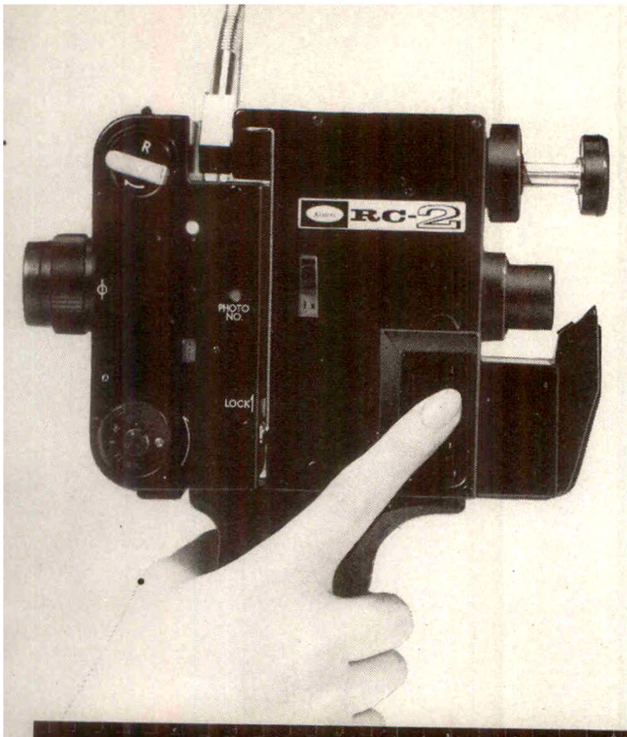
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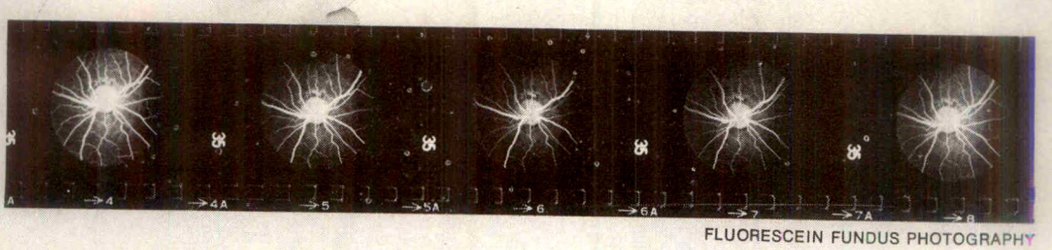
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# Kowa RC-2

## fundus camera

*The simple approach to fundus and fluorescein photography.*




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• To be fully meaningful to the medical profession, all instrumentation must function as an extension of the user's eyes, hands, and mind. The Kowa RC-2 fundus camera fully embodies this principle.

• *Fundus and External Photography* The basic RC-2 incorporates every conceivable advance in optics, mechanics, and electronics. Standard are built-in flash, 2X magnifying lens, automatic frame numbering for patient coding, and more. It will produce impeccable 35mm results even for inexperienced users.

• *Fluorescein Photography* By simply adding an auto-wind back, filters, and a quick-cycling power unit, the RC-2 becomes a flawless fluorescein photographic instrument.

• *Polaroid® Photography* An attachment gives you 60-second fundus photographs.

To see why the *total systems approach* has made Kowa's RC-2 the standard by which all others are measured, contact the representative in your area.

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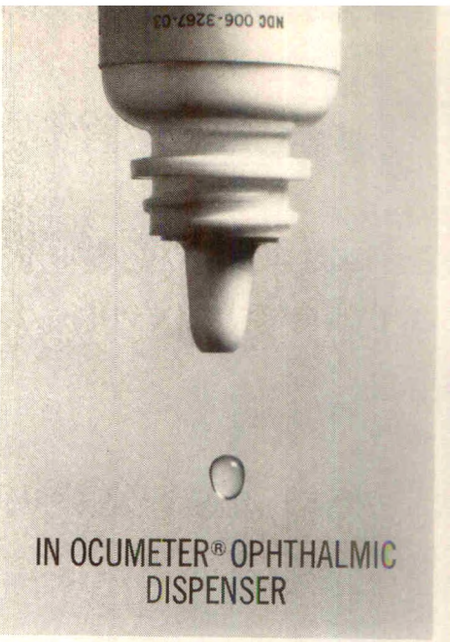
## in open-angle glaucoma

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## (DEMECARIUM BROMIDE | MSD)

OPHTHALMIC SOLUTION, 0.125% and 0.25%

## the cholinesterase inhibitor that needs no pampering




IN OCUMETER® OPHTHALMIC DISPENSER

**FOR TOPICAL APPLICATION INTO THE CONJUNCTIVAL SAC ONLY**

**Contraindications:** Known hypersensitivity; active uveal inflammation; most cases of narrow-angle glaucoma.

**Warnings:** Should be administered with extreme caution to patients with myasthenia gravis who are on systemic anticholinesterase therapy; conversely, systemic anticholinesterase drugs for myasthenia gravis should be added cautiously. Succinylcholine should be administered with extreme caution before or during general anesthesia, because of possible respiratory and cardiovascular collapse.

*Use in Pregnancy:* Safe use in pregnancy has not been established, nor has the absence of adverse effects on the fetus or on respiration of the neonate. During pregnancy weigh potential benefits against possible hazards.

**Precautions:** Gonioscopy is recommended before therapy. Do not use, or use cautiously, when an intraocular inflammatory process is present.

Compression of the lacrimal sac during and following instillation for a minute or two minimizes drainage into the nasal chamber. Wash hands immediately after instillation. Discontinue use if salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, or cardiac irregularities occur.

Persons exposed to organophosphate-type insecticides and pesticides (gardeners, organophosphate-manufacturing plant or warehouse workers, farmers, residents of communities which are undergoing insecticide spraying or dusting, etc.) should be warned of added systemic effects possible from absorption through the respiratory tract or skin. Wearing of respiratory masks, frequent washing, and clothing changes may be advisable.

Use with extreme caution, if at all, in patients with marked vagotonia, bronchial asthma, spastic gastrointestinal disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent myocardial infarction, epilepsy, parkinsonism, and other disorders that may respond adversely to vagotonic effects. Use extreme caution before intraocular surgery because of the possibility of hyphema.

Despite observance of all precautions, repeated administration may cause depression of the concentration of cholinesterase in the serum and erythrocytes, with resultant systemic effects.

**Adverse Reactions:** Stinging, burning, lacrimation, lid muscle twitching, conjunctival and ciliary redness, brow ache, headache, and induced myopia with visual blurring; activation of latent iritis or uveitis; retinal detachment has been reported occasionally. Iris cysts may form, enlarge, and obscure vision, more frequently in children; cysts usually shrink when the miotic is discontinued but, rarely, may rupture or break free into the aqueous. Frequent examination is advisable.

Prolonged use may cause conjunctival thickening and obstruction of nasolacrimal canals. If systemic effects occur (e.g., salivation, urinary incontinence, nausea, abdominal cramps, vomiting, diarrhea, dyspnea, bradycardia, cardiac irregularities), parenteral administration of atropine is indicated: 0.4 to 0.6 mg or more for adults, proportionately less for children; artificial respiration may be required. Similar therapy is indicated for overdosage.

Lens opacities have been reported, and routine slit-lamp examinations should accompany prolonged use. Paradoxical increase in intraocular pressure may occur and be alleviated by a mydriatic.

**Dosage and Administration:** Initial titration and dosage adjustments must be individualized to obtain maximal therapeutic effect. Patient must be observed closely during initial period. If response is not adequate within first 24 hours, consider other measures. Keep frequency of use to a minimum in all patients, but especially in children.

Since technic is crucial to proper and safe administration, consult Direction Circular for full details.

**Supplied:** In 5-cc OCUMETER® Ophthalmic Dispenser containing 0.125 or 0.25 percent solution and sodium chloride; benzalkonium chloride 1:5000 added as preservative.

*For more detailed information, consult your MSD representative or see the Direction Circular. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486*

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# in post-operative retinal or cataract surgery

## Murocoll Phenylephrine, Scopolamine and Prednisolone (Murocoll Product #2c)

**FORMULA:** Sterile ophthalmic solution containing Phenylephrine Hydrochloride 10%, Scopolamine Hydrobromide 0.3% and Prednisolone 0.2%; preservatives chlorobutanol 0.5%; sodium bisulfite; polysorbate 20 and distilled water as inactive ingredients.

**CLINICAL INDICATIONS:** Used in intraocular inflammation such as uveitis and iritis, where it is desirable to maintain dilation, rest ciliary body as well as to decrease inflammation with post-operative retinal or cataract surgery.

**CONTRAINDICATIONS:** (a) Acute herpes simplex, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva. (b) Tuberculosis. (c) Fungal diseases. (d) Acute purulent untreated infections which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid. (e) Purulent conjunctivitis and purulent blepharitis. Individuals with hypersensitivity to belladonna alkaloids.

**PRECAUTIONS:** (a) Extended use of topical steriod therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. (b) In those diseases causing thinning of the cornea, perforation has been known to have occurred with the use of topical steroids.

**CAUTION:** Should be used with caution in patients with narrow chamber angles.

**DOSAGE:** One or two drops in eye three or four times daily until all signs of intraocular inflammation are absent.

Use of this combination reduces the number of instillations that would be required if separate agents were prescribed, and materially reduces the cost of therapy.

**AVAILABLE:** 7.5 cc glass bottle with plastic dropper on prescription only.

**Complete ophthalmologic formulary available on request**

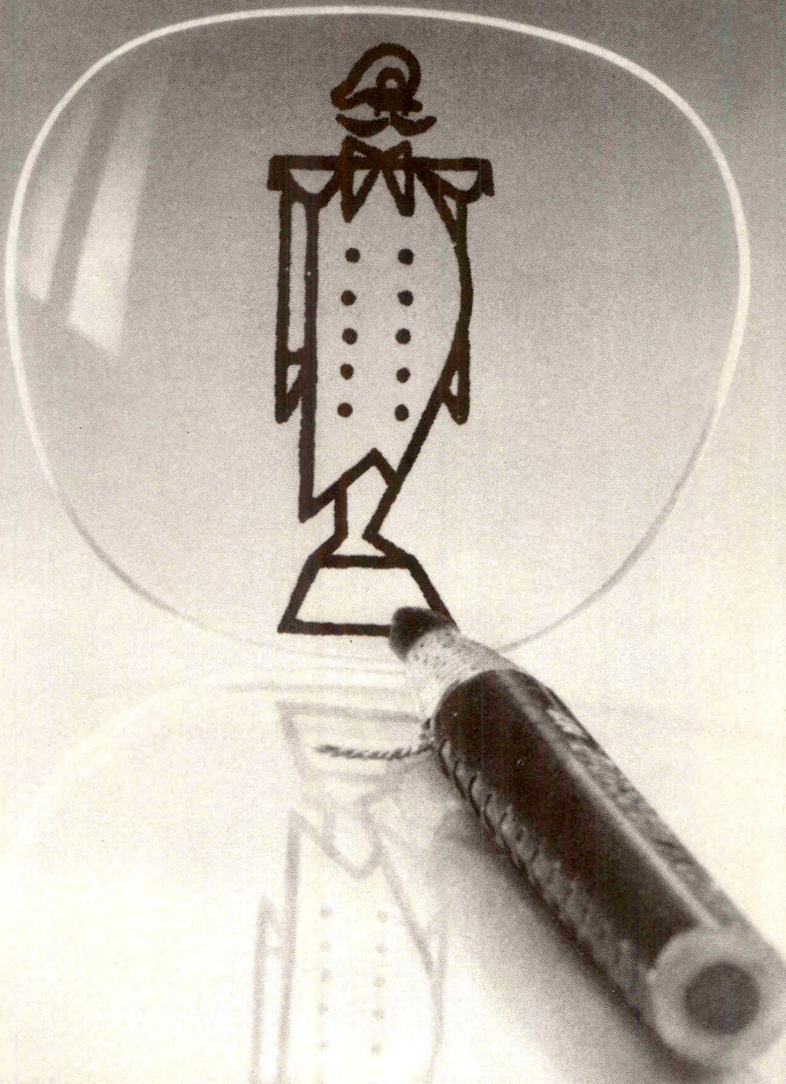
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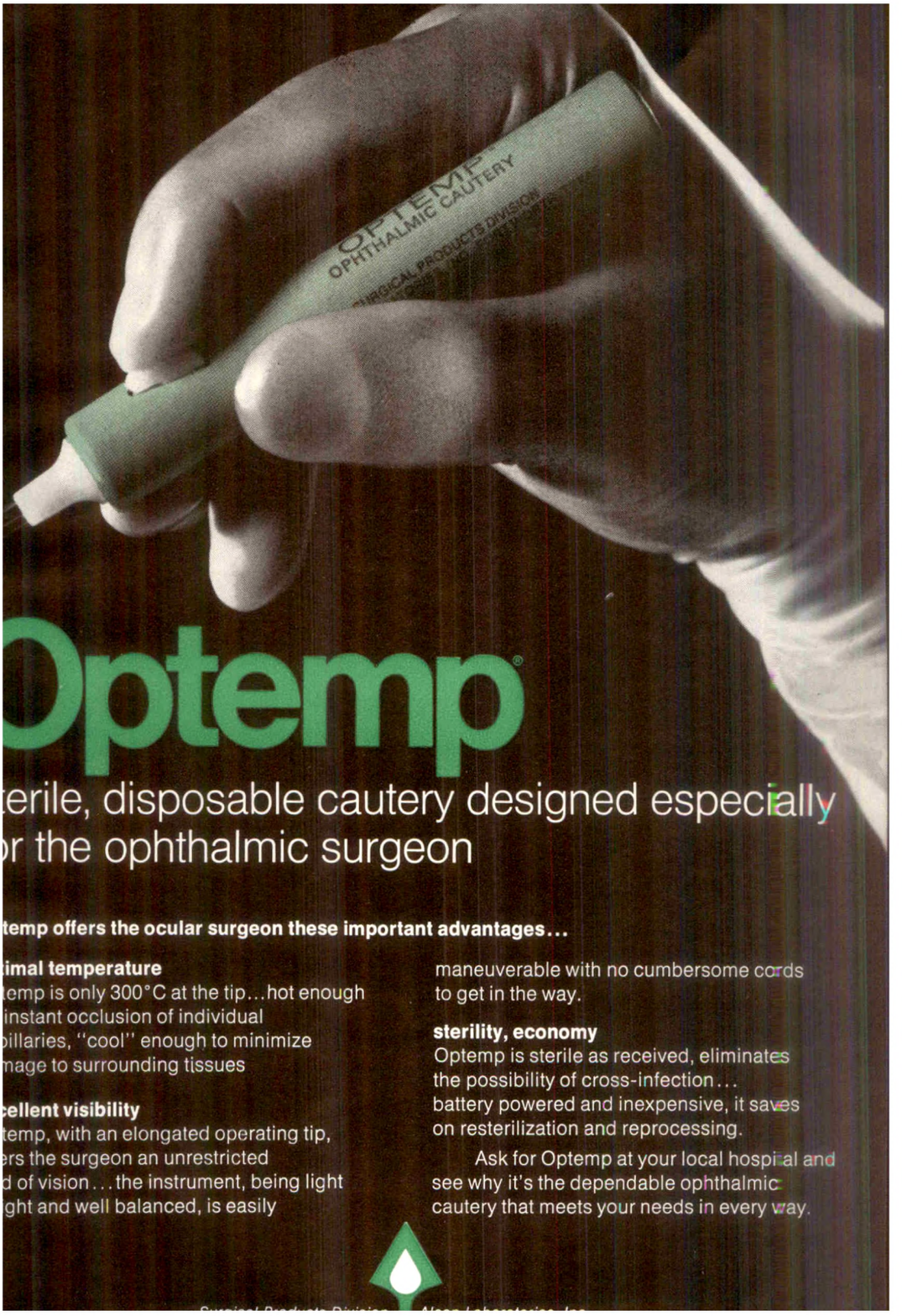
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**temp offers the ocular surgeon these important advantages...**

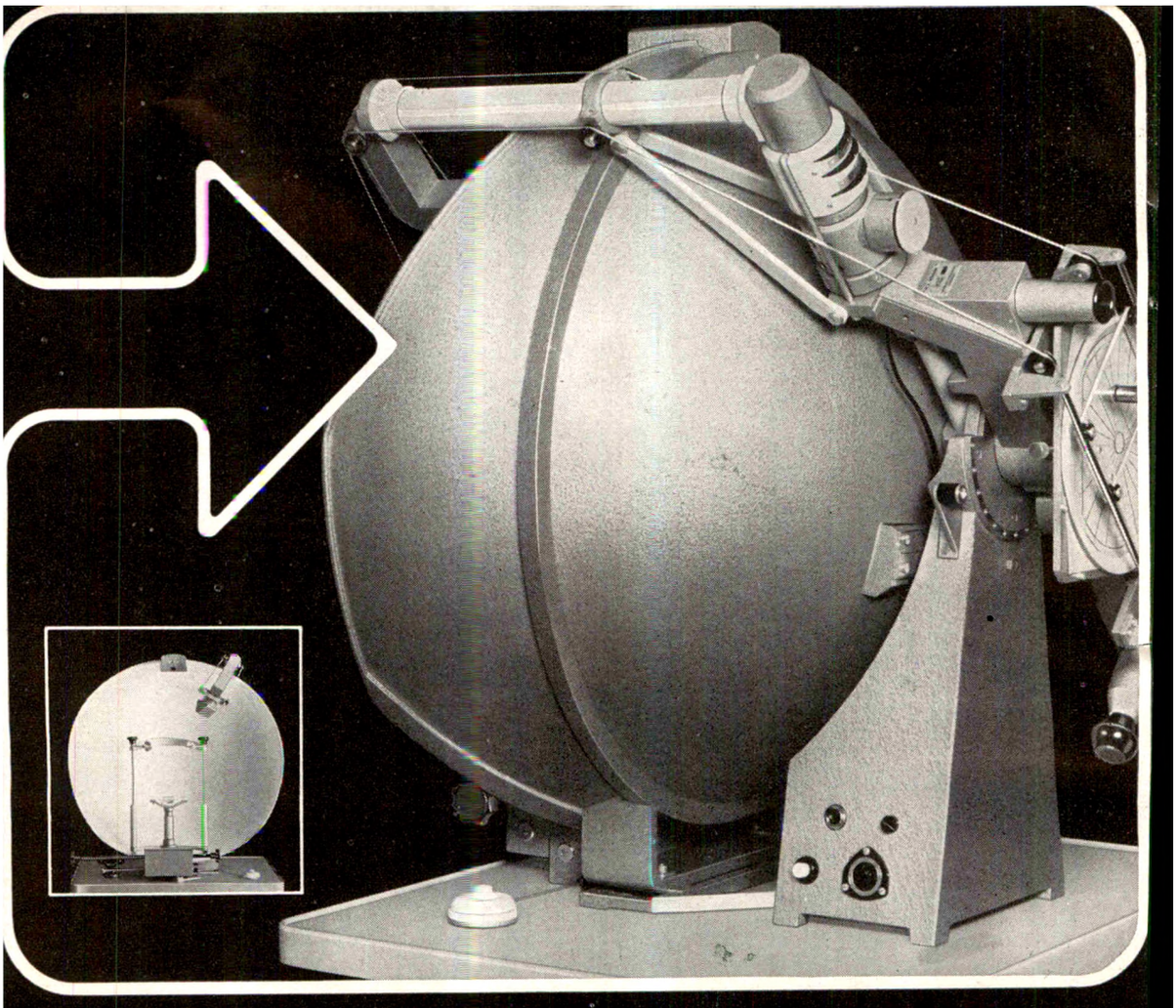
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temp is only 300°C at the tip...hot enough instant occlusion of individual pillaries, "cool" enough to minimize mage to surrounding tissues

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**sterility, economy**
Optemp is sterile as received, eliminates the possibility of cross-infection... battery powered and inexpensive, it saves on resterilization and reprocessing.

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# Projection Perimeter

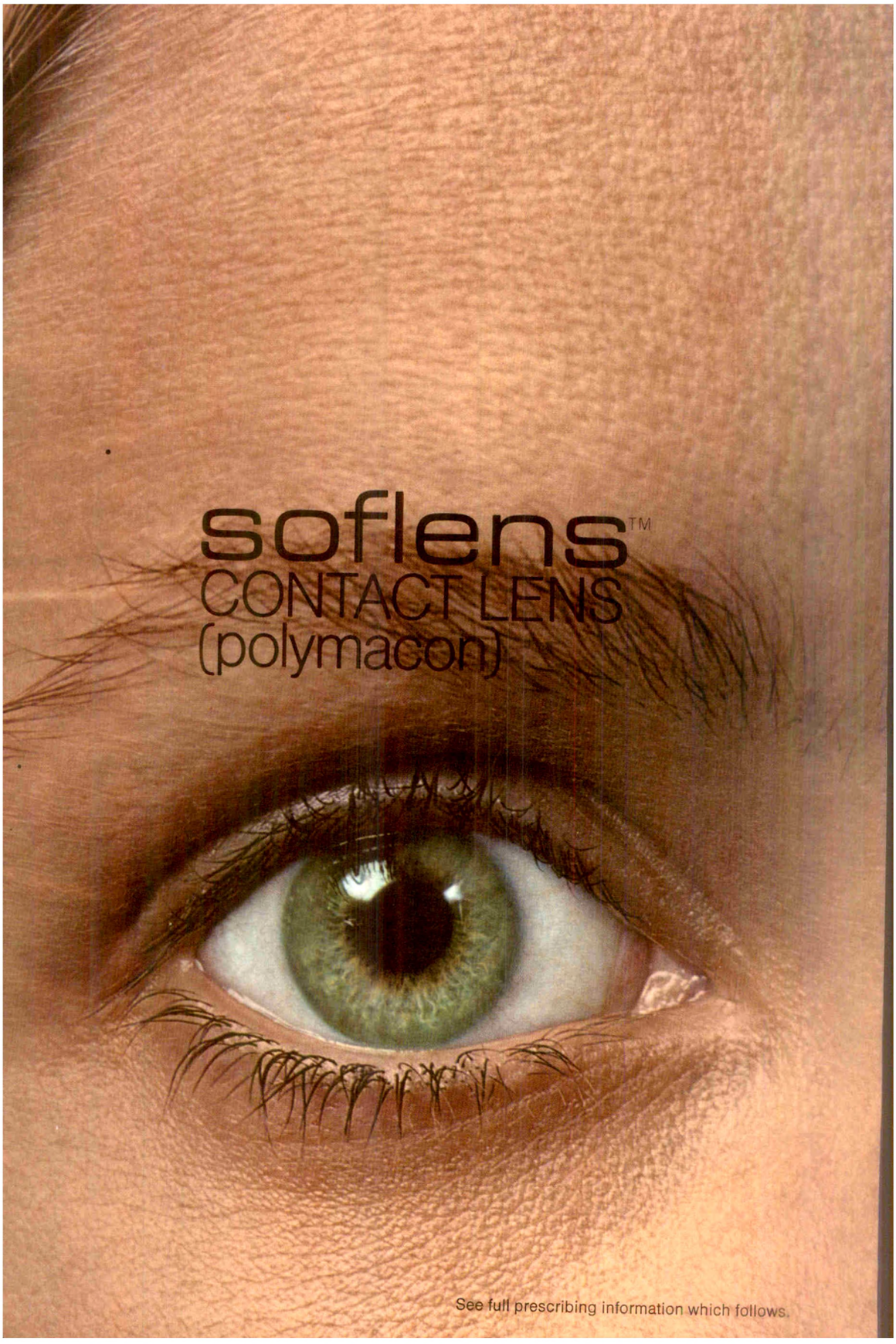
- Evenly illuminated perimeter surface with identical retina-congruent distances at all angles
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soflens™
CONTACT LENS
(polymacon)
See full prescribing information which follows.



# comfort... from the beginning

# soflens
## CONTACT LENS (polymacon)

Conventional methods of fitting contact lenses do not apply to SOFLENS Contact Lenses (polymacon). For a detailed description of the fitting technique, refer to the SOFLENS Fitting Guide, copies of which are available from: SOFLENS Division, Bausch & Lomb Incorporated, Rochester, New York 14602.

**DESCRIPTION:** The SOFLENS Contact Lens (polymacon) is a hemispherical shell of approximately 13mm chord diameter and 0.1 to 1.0mm thickness. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The SOFLENS Care Kit is a package required for lens asepticizing, cleaning, and storage consisting of the following:

| | |
|---|---|
| SOFLENS Carrying Case | Cat. #140301 |
| SOFLENS Aseptor-Patient Unit | Cat. #140302 |
| SOFLENS Squeeze Bottle | Cat. #140304 |
| SOFLENS Salt Tablets | Cat. #140305 |
| SOFLENS Patient Instruction Book | Cat. #140300-100 |

**ACTIONS:** The SOFLENS Contact Lens (polymacon) absorbs water to 38.6% of its dry weight when equilibrated in normal saline solution. In its hydrated state a SOFLENS Contact Lens (polymacon) becomes soft and pliable. When placed on the human cornea the hydrated SOFLENS Contact Lens (polymacon) acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

**INDICATIONS:** SOFLENS Contact Lenses (polymacon) are indicated for the correction of visual acuity in persons with non-diseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

**CONTRAINDICATIONS:** SOFLENS Contact Lenses (polymacon) are contraindicated by the presence of any of the following conditions. (1) Acute and subacute inflammations of the anterior segment of the eye. (2) Any eye disease which affects the cornea or conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses. (6) Early stages of pregnancy.

**WARNINGS: Medicants and Eye Drops**—SOFLENS Contact Lens (polymacon) must be stored ONLY in normal saline solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by SOFLENS Contact Lens (polymacon) wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than normal saline may be used on SOFLENS when the lens is off the eye.
**Abrasions and Infections**—If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.
**Wearing Restrictions**—SOFLENS Contact Lenses (polymacon) should be removed before sleeping or swimming and in the presence of noxious and irritating vapors.
**Visual Blurring**—When visual blurring occurs the lens must be removed until the condition subsides.
**Lens Sanitation**—Patients who would not or could not adhere to recommended daily sanitary care of SOFLENS Contact Lenses (polymacon) should not be provided with them.

**PRECAUTIONS: Storage**—SOFLENS Contact Lenses (polymacon) must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be soaked in normal saline solution until it returns to a soft, supple state.
**Cleaning and Asepticizing**—SOFLENS Contact Lenses (polymacon) must be BOTH cleaned and asepticized daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. ASEPTICIZING with the SOFLENS Aseptor-Patient Unit has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the SOFLENS Carrying Case. Fresh normal saline must be prepared daily for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before asepticizing the lenses. If a SOFLENS Aseptor-Patient Unit is not available for asepticizing the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.
**Hygiene**—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.
**Fluorescein**—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

**ADVERSE REACTIONS:** Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline and wait until the lens moves freely before removing it. Clinical studies indicate visual blurring is experienced by less than 5% of SOFLENS Contact Lens (polymacon) wearers. Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

**DOSAGE AND ADMINISTRATION:** There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

| Day | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) |
|---|---|---|---|---|---|
| 1 | 3 | 1 | 3 | 1 | 3 |
| 2 | 3 | 1 | 3 | 1 | 3 |
| 3 | 4 | 1 | 4 | 1 | 4 |
| 4 | 4 | 1 | 4 | 1 | 4 |
| 5 | 6 | 1 | 6 | 1 | 4 |
| 6 | 6 | 1 | 6 | 1 | 4 |
| 7 | 8 | 1 | 8 | | |
| 8 | 8 | 1 | 8 | | |
| 9 | 8 | 1 | 8 | | |
| 10 | 10 | 1 | balance of the waking hours* | | |
| 11 | 12 | 1 | balance of the waking hours* | | |
| 12 | 14 | 1 | balance of the waking hours* | | |

*Lenses should never be worn 24 hours a day.

Care must be taken on the initial visit to assure that the patient is supplied with a SOFLENS Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

**HOW SUPPLIED:** Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the dioptric power (black for plus power lenses; red for minus) and the manufacturing lot number of the lens. To assure proper lens care and handling, each SOFLENS patient must be supplied with a complete SOFLENS Care Kit.

**BAUSCH & LOMB**
SOFLENS DIVISION

Specific for
Herpes Simplex Keratitis

**STOXIL®**
**brand of IDOXURIDINE**

the only brand of IDU
available in two forms:
Solution—Ointment

Both now available in Canada




# The choice is yours

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

**Indications:** Only in the treatment of herpes simplex keratitis.

**Description: 'Stoxil' Ophthalmic Solution** contains idoxuridine (5-iodo-2'-deoxyuridine) **0.1% (1 mg./ml.)** in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. **'Stoxil' Ophthalmic Ointment** contains idoxuridine **0.5% (5 mg./gram)** in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

**Contraindications:** Contraindicated in patients with known or suspected hypersensitivity to any of its components.

**Precautions:** Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

**Adverse Reactions:** Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

**How Supplied:** 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

**Stability:** The Solution should be stored in refrigerator until dispensed. The Ointment does not require refrigeration.

SK&F Smith Kline & French Laboratories

# A little innovation is a big help

**Nothing is quite as satisfying as finding a new way to help the patient.**

**You will help a beginning presbyope** adjust to his bifocal correction by simply adding Press-On™ lenses to his present single vision spectacles. The interim Press-On lenses establish usefulness and acceptance. Also, they will help determine the proper seg height, shape and size before the permanent Rx is produced.

**Reading aids for low vision patients** have been a real problem. Adds above +3.00 have been impractical for everybody concerned. Press-On lenses give you bifocal segments of any size and shape incorporating proper prism to insure comfortable binocular vision. They can be applied in minutes.

**Post-operative cataract patients** are apprehensive. Wouldn't it be a happy innovation to hand these patients their own comfortable glasses with an interim aspheric Press-On lens correction that provides a panoramic field of view. They will see better and look better, immediately.

These are a few examples. Clip the coupon, and we'll send you more ideas plus a Press-On lens for your own use.

All OSG Fresnel lenses provide optimum asphericity regardless of power.

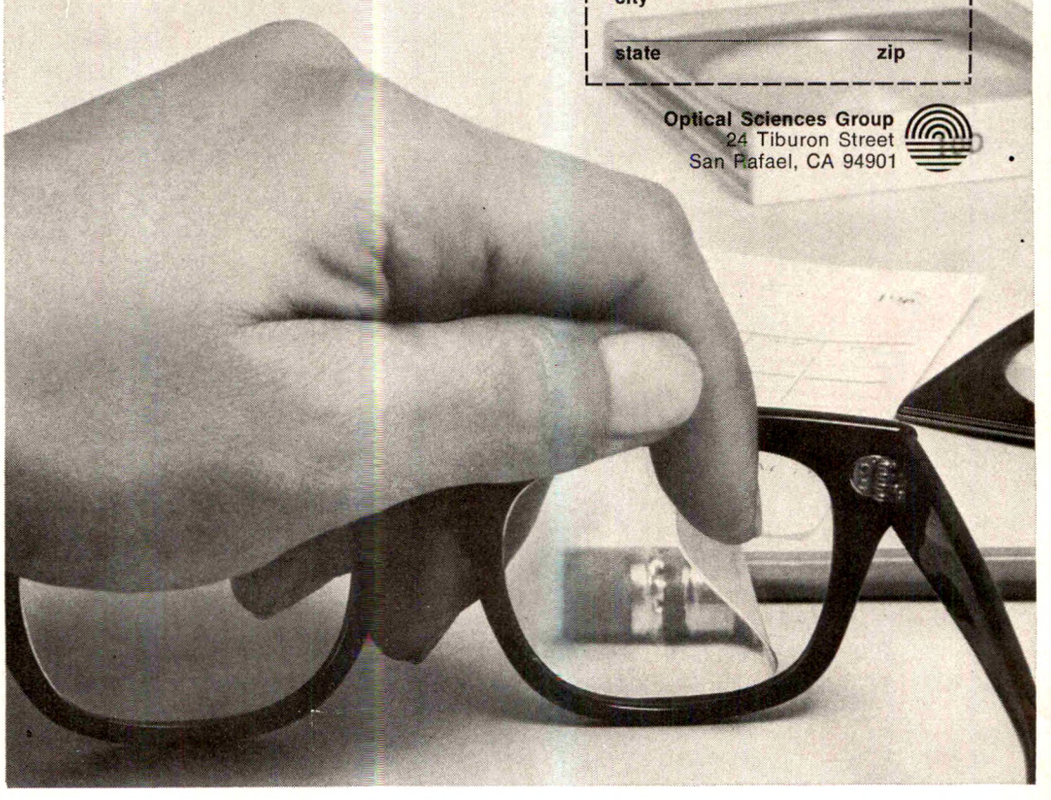
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**Optical Sciences Group**
24 Tiburon Street
San Rafael, CA 94901



# The new Zeiss Zoom OpMi 7... a true ophthalmological specialist.

The new OpMi 7 is truly special in every sense of the word. It's special in that it is designed only for ophthalmological microsurgery. And special too in price—its many outstanding design features are shared only with instruments costing considerably more.

**Wide field of view:** 55 mm at 3.6x — 95% more area than other instruments in its price range.

**Building block design:** it accepts all the valuable Zeiss accessories, including the Beam Splitter System for still and motion picture photography and TV, the unique high-eyepoint eyepieces for spectacle wearers, a fiber-optic "cool-light" illumination system, the assistant's stereo microscope with the same high quality optics as the surgeon's, and the 2x operating field magnifier.

**Choice of 3 stands:** including the new Ceiling Suspension System.

**Choice of 3 working distances:** 6", 7" or 8" to your specification.

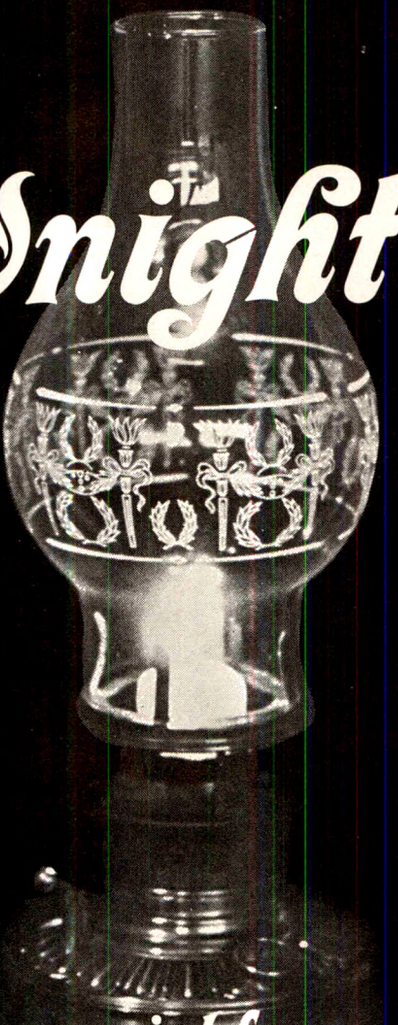
That's only a start. For complete details, write or call Carl Zeiss, Inc., 444 5th Ave., New York, N. Y. 10018. (212) 736-6070.

Nationwide Service.

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# Midnight Oil



## Something special from Armorlite!

*From the time we introduced our flat-top trifocals, they were so successful that we could not keep up with the demands. It has taken us years to catch up, but we finally made it.*

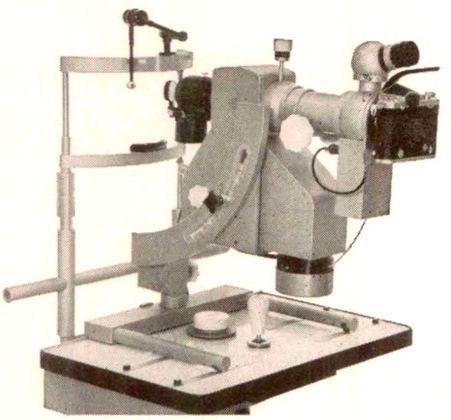
*These are the finest hard resin trifocals that money and care can produce. So, when your patient needs the intermediate range of our popular flat-top (or old style round) trifocal, our distributors will have the required lenses in stock.*

*We won't back order them anymore, but we will keep our lamp handy . . . just to remind us what it's like when we get behind in production.*

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THE ORIGINATORS OF HARD RESIN LENSES

# Look what fluorescein fundus photography can tell you.



This fluorescein angiogram of a diabetic retinopathy, revealing a gross vasculopathy in micro and macro vessels, is only one example of the results that can be easily obtained with the new Zeiss Fundus Flash II. Of the many features of this unique instrument, four are particularly worth citing here:

(1) The light source, adjustable for low, medium or high intensity, with low heat, fast recycling, short warm-up (0.5 sec.) and long flash tube life.

(2) The built-in digital data timing system which indicates automatically the time lapse between photographs.

(3) The control system which allows preselection of frame sequences from 1 to 4 frames/sec., time exposures, and automatic shutoff of film transport after a selected number of frames.

(4) The exclusive Allen Stereo Separator for taking stereo photographs automatically with no equipment adjustment.

For complete details on the many other features of this easy-to-use instrument, write Carl Zeiss, Inc., 444 5th Avenue, New York, N.Y. 10018.

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THE GREAT NAME IN OPTICS

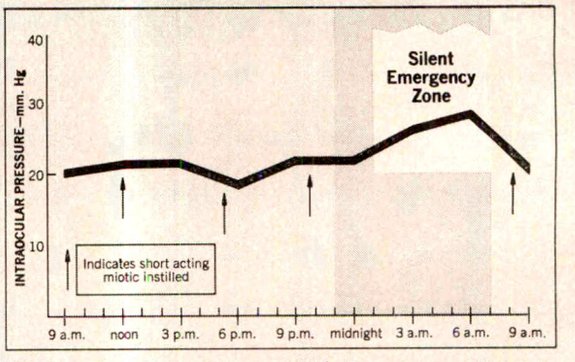
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# Not more potent, but longer acting*...

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

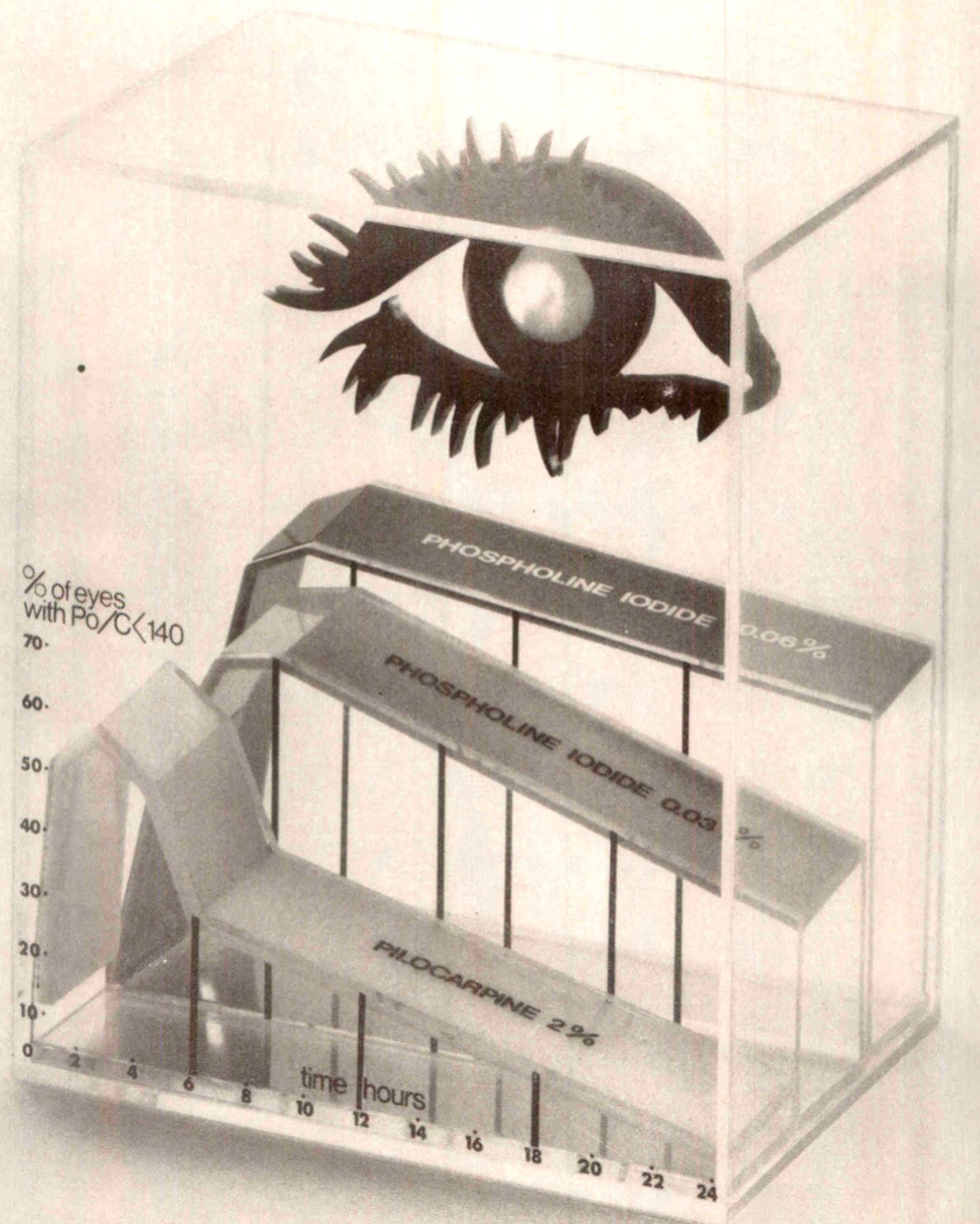



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25% —when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

for 24 hour control in chronic simple (open-angle) glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, brow-ache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

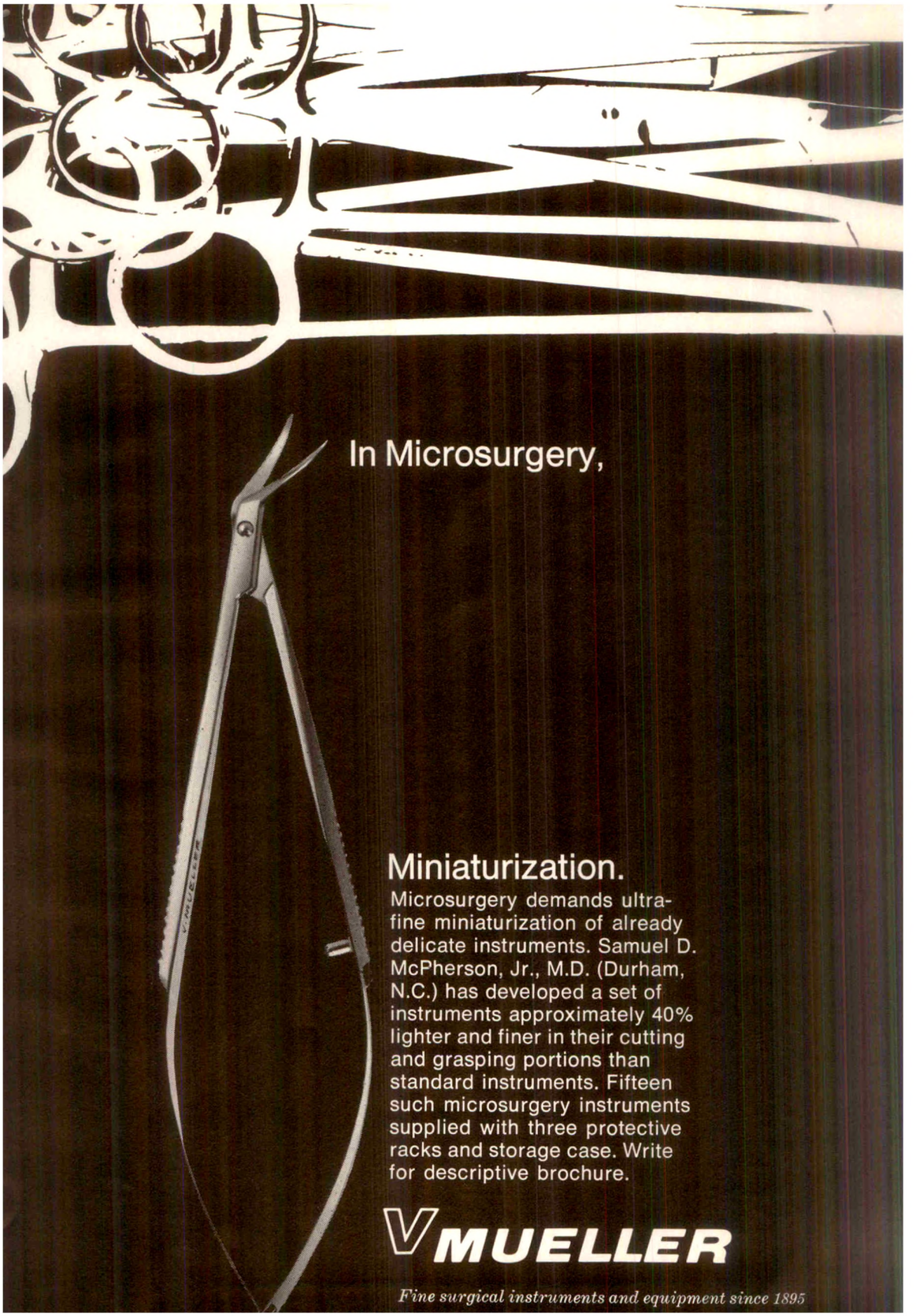
Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017



In Microsurgery,

## Miniaturization.

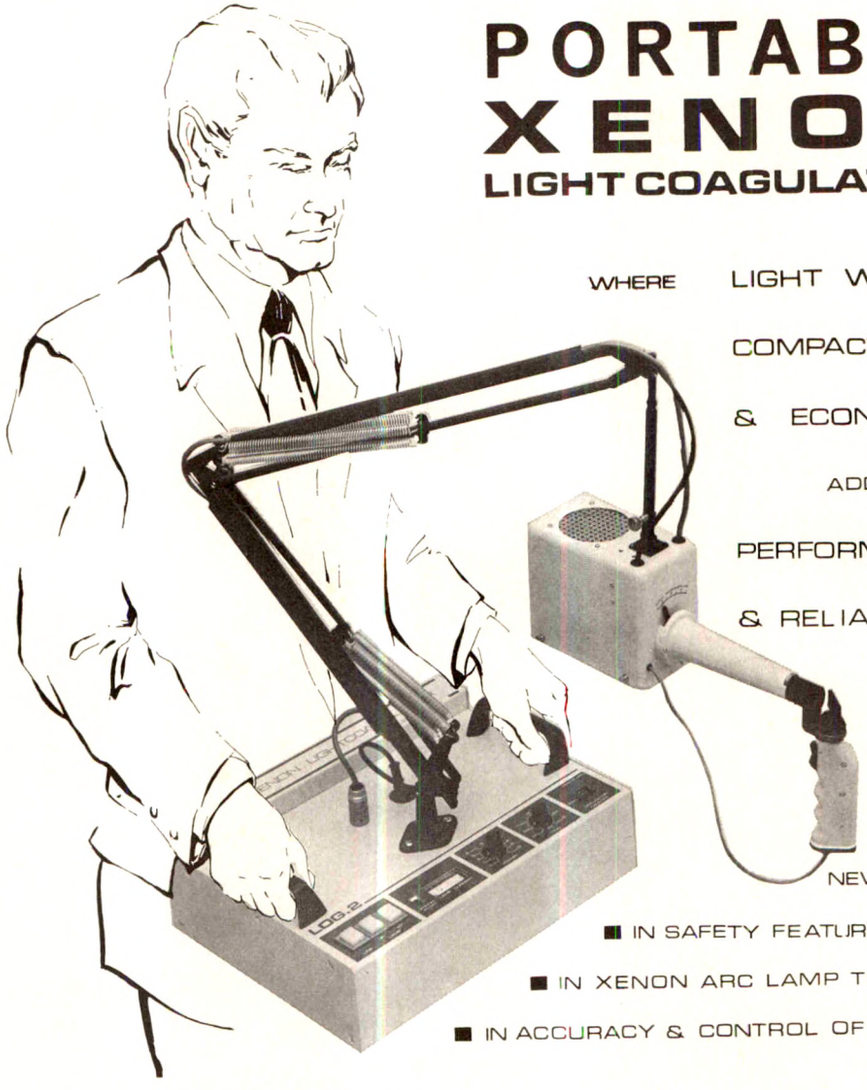
Microsurgery demands ultra-fine miniaturization of already delicate instruments. Samuel D. McPherson, Jr., M.D. (Durham, N.C.) has developed a set of instruments approximately 40% lighter and finer in their cutting and grasping portions than standard instruments. Fifteen such microsurgery instruments supplied with three protective racks and storage case. Write for descriptive brochure.

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*Fine surgical instruments and equipment since 1895*

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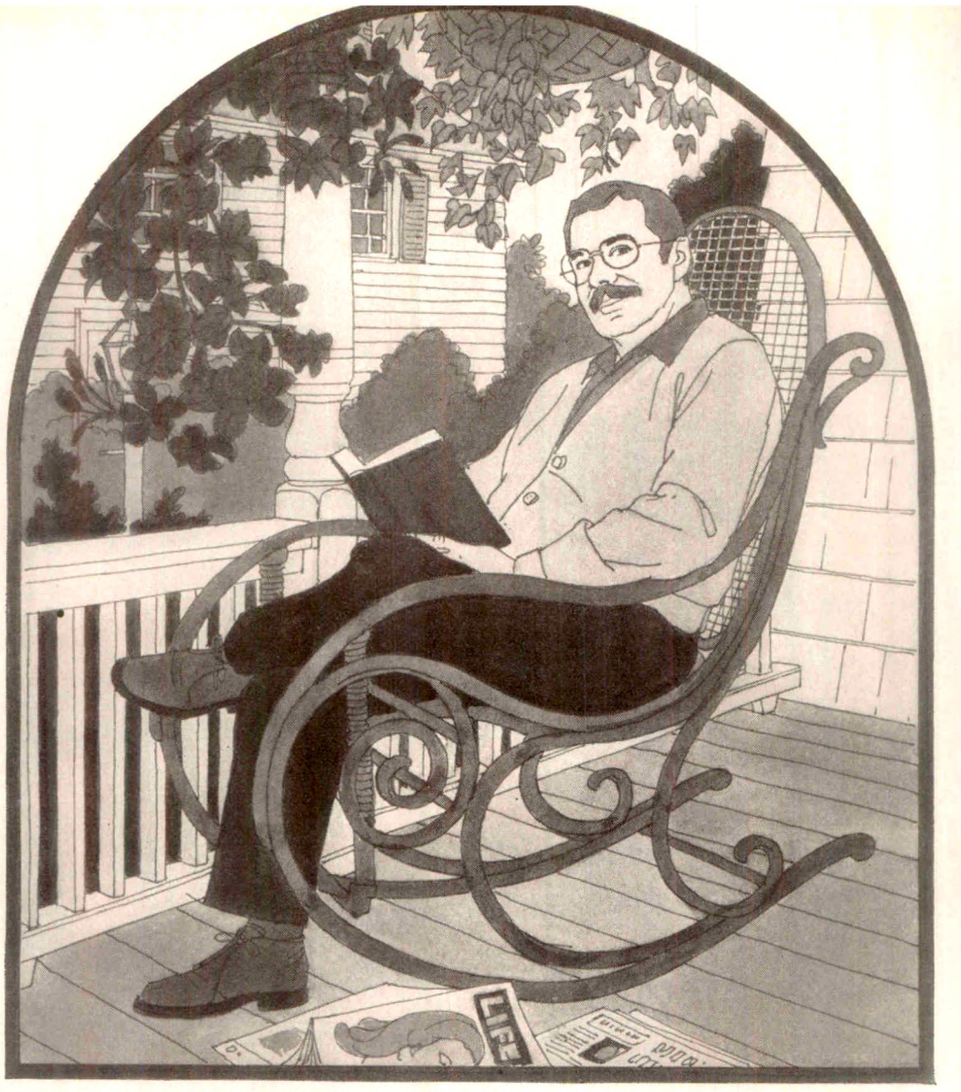
WHERE LIGHT WEIGHT COMPACTNESS & ECONOMY ADD TO PERFORMANCE & RELIABILITY.

NEW APPROACH

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And DIAMOX does not interfere with other forms of glaucoma therapy which influence the outflow mechanism. In fact, a complementary effect may be obtained when DIAMOX is used in conjunction with miotics.

Treatment with DIAMOX may retard progress of glaucoma by reducing secretion of aqueous humor and thus intraocular pressure. With DIAMOX SEQUELS, acetazolamide is slowly released, and concentrations peak at 8 to 12 hours. A single dose may provide a therapeutic effect for as long as 18 to 24 hours. It is thus possible to maintain the inhibitory effect on aqueous humor formation with a twice-daily regimen . . . an important consideration for the patient's rest and for minimization of side effects.

# DIAMOX®
## ACETAZOLAMIDE
# SEQUELS® 500 mg
## Sustained Release Capsules

**ontraindications**—Situations in which sodium and/or potassium serum evels are depressed, in kidney and liver disease or dysfunction, supra-enal gland failure and hyperchloremic acidosis. Long-term administration contraindicated in chronic noncongestive angle closure glaucoma.

**arning**—Although teratogenic and embryocidal effects demonstrated in ice at more than ten times the equivalent therapeutic doses have not een evidenced in humans, DIAMOX Acetazolamide should not be used in regnancy, especially during the first trimester, unless the expected enefits outweigh these potential adverse effects.

**recautions**—Increasing the dose may increase drowsiness and paresthesia and decrease diuresis. Reactions common to sulfonamides may occur: fever, rash, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis. If such occur, discontinue drug and institute appropriate therapy.

**Side Effects**—During short-term therapy: paresthesias, loss of appetite, polyuria, drowsiness, confusion. In long-term therapy an acidotic state may supervene. Transient myopia has been reported. Other occasional reactions: urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, convulsions. 354-1

Lederle LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York 10965

# THE 10 MOS
# QUESTIONS ABOU

## THE QUESTIONS

1. What makes PHOTOGRAY lenses work?
2. How fast do PHOTOGRAY lenses change?
3. Will the darkening-fading process wear out?
4. Do PHOTOGRAY lenses need breaking in?
5. Can PHOTOGRAY lenses be hardened or toughened?
6. How do PHOTOGRAY lenses work in a car?
7. In what types of lenses is PHOTOGRAY glass available?
8. Is the darkening-fading process comfortable to the wearer?
9. Do PHOTOGRAY glasses have a residual tint indoors?
10. Will PHOTOGRAY glass be available in a darker sunglass version?

**Note:** If you get asked other questions by your patients about PHOTOGRAY glasses that you think would be of broad interest, please send them to us. When we get enough new ones, we'll answer them in another ad.

If you'd like complete technical information on PHOTOGRAY lenses, just write to: Corning Optical Products Dept., Corning, New York 14830.

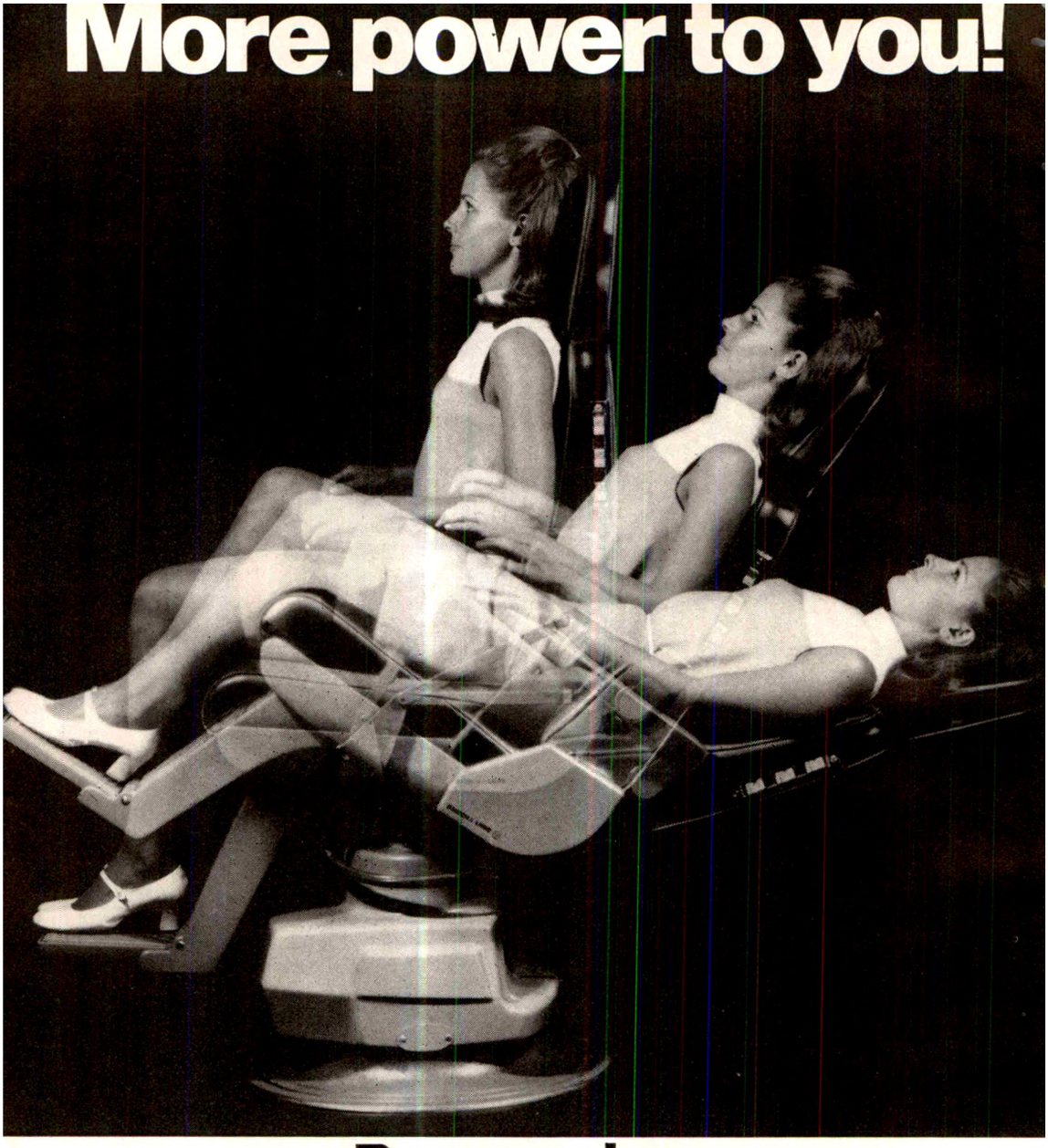
# )FTEN ASKED
# PHOTOGRAY® LENSES.

## THE ANSWERS

1. PHOTOGRAY lenses are photochromic: sensitive to ultraviolet light. When sunlight strikes them, invisible microcrystals of silver halide become darkened. When the light is removed, the crystals clear again.
2. Quite rapidly. In 60 seconds the lens is 75% darkened by sunlight and virtually fully darkened in 5 minutes. Removed from sunlight the lens clears half way in 5 minutes and 75% in 20 minutes. At their darkest, PHOTOGRAY lenses have a light transmittance of 45%. When clearest they have a light transmittance of 85%.
3. No. The photochromic reaction is locked into the composition of the glass and is completely reversible. It will keep performing for a lifetime without changing its characteristics.
4. Yes. Several complete darken-fade cycles are needed to bring PHOTOGRAY lenses up to their normal operating performance.
5. Yes, Most definitely. PHOTOGRAY lenses can be heat-treated or tempered. The tempering time is slightly different from that needed for clear lenses. Corning publishes heat-treating tables that give settings for the more popular units available.
6. Not too well. The window glass will screen out a lot of the ultraviolet light which activates the photochromic property of the lenses. This keeps the glass from darkening as fully as when it is exposed to direct sunlight.
7. PHOTOGRAY lenses come in a full range of sizes—in both single-vision and 1 piece multi-focal types.
8. Yes. The process, while quite rapid, is gradual enough to be imperceptible to the wearer. This, combined with the protection given by the darkened glass, is why PHOTOGRAY is known as the "comfort glass".
9. Yes. It's a very light, hardly noticeable tint.
10. Yes. Corning is currently in the final stages of developing a sunglass companion to PHOTOGRAY glass. Called PHOTOSUN™ glass, it's a true variable sunglass. PHOTOSUN lenses will be ready for introduction shortly.

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# More power to you!



## Power-poise Ophthalmic Chair by Bausch & Lomb

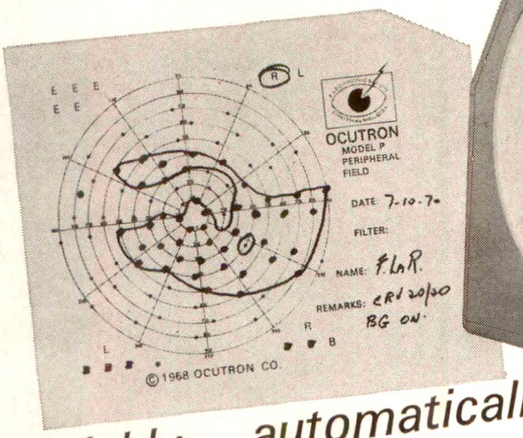
e Power-poise Chair is a prime ex-
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able in an attractive selection c
four standard enamel and four standard Naug
hyde upholstery colors plus an additional eleve
distinctive optional Naugahyde upholstery color
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BAUSCH & LOMB

# *Now* OCUTRON®

## *offers you visual fields*

...whenever you want
...as often as you want
without your being there






## *quickly... automatically!*

U.S. Patent Nos. 3,288,546
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The Ocutron® Visual Field Tester, developed by a leading ophthalmologist, is a highly precise electronic instrument that automatically examines the visual field and records it permanently on the standard chart that you are accustomed to using and interpreting.

Without the presence of doctor or nurse, the patient tests himself by push-button response to stimuli of standard light targets as they appear within the white hemisphere. This response is electrically registered on the chart.

Difficult and time-consuming fields like the above glaucoma field are as easily and quickly tested as a simple normal field.

Background may be lighted or not, as desired, for light or dark adapted fields. Built-in check on patient fixation and patient reliability.

Particularly suitable for high volume performance. Simple enough for screening. Accurate enough for definitive, repeatable field study.

For further information write for new literature
or contact your ophthalmic distributor.

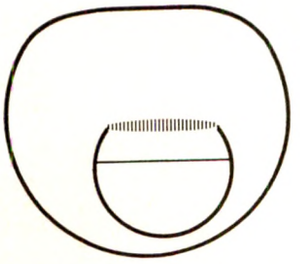
ELECTRONICS FOR OPHTHALMOLOGY

## OCUTRON COMPANY

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# Some lenses have everything:

Variable seg widths
Distortions in the segs
Cylinder in the segs
ouble curves on front side
Bubbles in the interface
Waves on the front surface
Fracture
Gray
Pit
Abuse
Loose tolerances
Polishing out
Bad contact
Bad line
Bad glass
Underside surface
Chip
Depressed segment
Tilted segment
Locked-in light
Surface light
Water marks
Fume
Halo



## Sentinel has none of the

136 separate inspection procedures make tain that every defective lens is elimin All that passes through this tight inspe screen are pure, perfect Sentinel Le Make sure you get the best; look for the tinctive Sentinel identification on the u side of the segment shelf. (It appears barely visible series of evenly spaced li

**Univi**

developer of Senti
the quality-identifie

a subsidiary of Itek Cor

# A singular new antibiotic for the eye that works the way you think it should

## GARAMYCIN® brand of GENTAMICIN SULFATE OPHTHALMIC SOLUTION/OINTMENT



Each cc. or gram contains gentamicin sulfate equivalent to 3.0 mg. gentamicin.

## You think it should have a wide antibacterial spectrum

GARAMYCIN's wide range of antibacterial action is equal to the spectrum commonly prescribed in the combinations of neomycin, polymyxin and bacitracin or gramicidin in the treatment of external eye infections due to susceptible organisms. It has activity against a wide variety of both gram-positive and gram-negative organisms, including the "difficult" ones—*Pseudomonas aeruginosa* strains and Proteus.

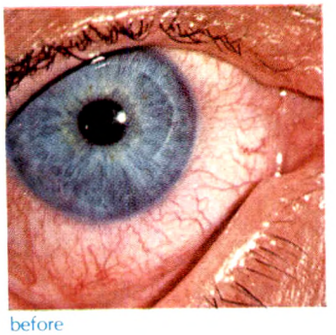
## You think it should be a single entity antibiotic

GARAMYCIN is a single entity antibiotic with a low incidence of sensitization or resistance*—can be used repeatedly with continued effectiveness, less concern about allergic potential (*Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.)

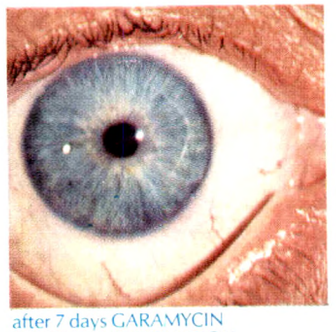
## You think it should be clinically effective

GARAMYCIN OPHTHALMIC has been described as appearing to be "...an antibiotic of choice for the initial treatment of external ocular infections."[1] It has "proved highly effective...for a wide variety of common bacterial eye infections..."[2] (due to susceptible organisms).
(1. Gordon, D.M.: Amer. J. Ophthal. 69:300 [Feb.] 1970. 2. Magnuson, R. H., and Suie, T.: JAMA 199:427 [Feb. 6] 1967.)

In acute catarrhal conjunctivitis and episcleritis† due to *Staphylococcus aureus* coagulase negative

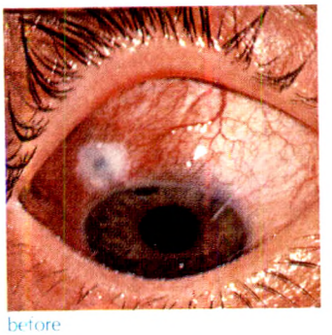


before



after 7 days GARAMYCIN OPHTHALMIC SOLUTION

In infected bleb (post-glaucoma surgery)† due to *Staphylococcus aureus* coagulase negative and *Streptococcus viridans*



before

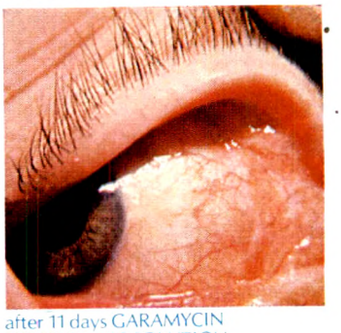


after 9 days GARAMYCIN OPHTHALMIC SOLUTION

In acute conjunctivitis and dacryocystitis†† due to pneumococcus



after 7 days GARAMYCIN OPHTHALMIC SOLUTION



after 11 days GARAMYCIN OPHTHALMIC SOLUTION

# New GARAMYCIN® ophthalmic

brand of GENTAMICIN SULFATE

SOLUTION/OINTMENT

†Photographs courtesy of D. Gordon, M.D., N.Y., N.Y. ††Photographs courtesy of S. Fox, M.D., Baltimore, Md.

# You think it should have flexibility in dosage forms

GARAMYCIN OPHTHALMIC SOLUTION, sterile, isotonic, and buffered to pH of tears, does not blur vision, is well suited to daytime use—supplied in an unbreakable, easy-to-handle dispenser.

GARAMYCIN OPHTHALMIC OINTMENT provides gentle emollient action and keeps medication in contact with tissues for longer periods. It is particularly advantageous for nighttime use or in non-ambulatory patients—supplied in easy-to-use ophthalmic tube.

## Clinical Considerations

**Description:** GARAMYCIN is an antibiotic of the aminoglycoside group active against a wide variety of pathogenic gram-negative and gram-positive bacteria.

GARAMYCIN Ophthalmic Solution is a sterile aqueous solution buffered to approximately pH 6.7 for use in the eye. Each cc. contains gentamicin sulfate (equivalent to 3.0 mg. gentamicin), disodium phosphate, monosodium phosphate, sodium chloride, and benzalkonium chloride as a preservative.

GARAMYCIN Ophthalmic Ointment contains, in each gram of ointment, gentamicin sulfate (equivalent to 3.0 mg. gentamicin), and methylparaben and propylparaben as preservatives in a bland base of clear petrolatum.

Although significant resistance in organisms isolated from patients treated with gentamicin has not occurred at the present time, this may occur in the future as resistance has been produced with difficulty *in vitro* by repeated exposures.

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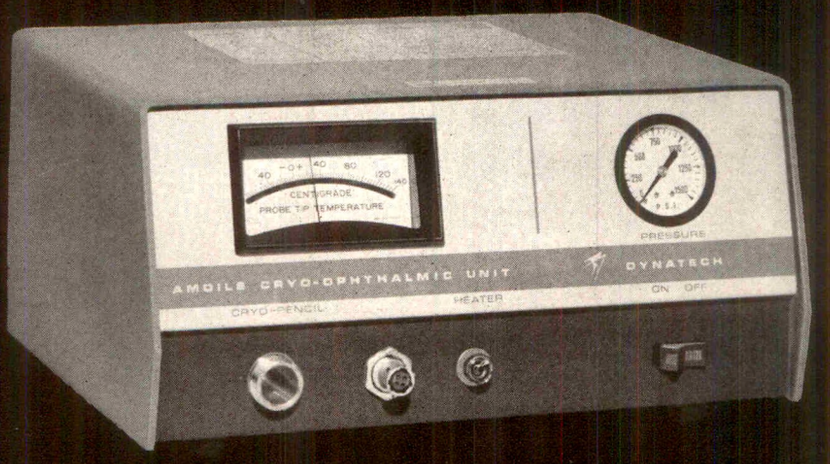
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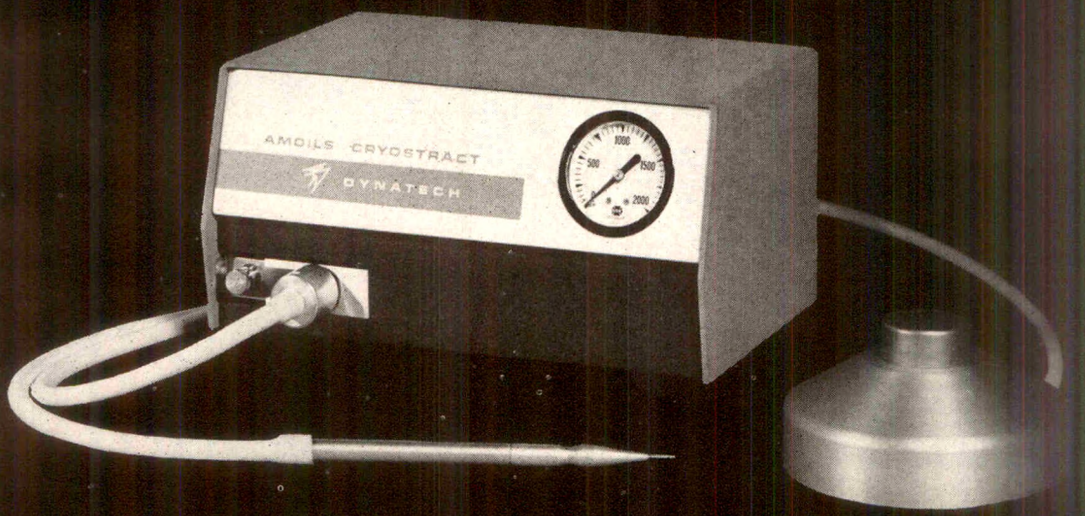

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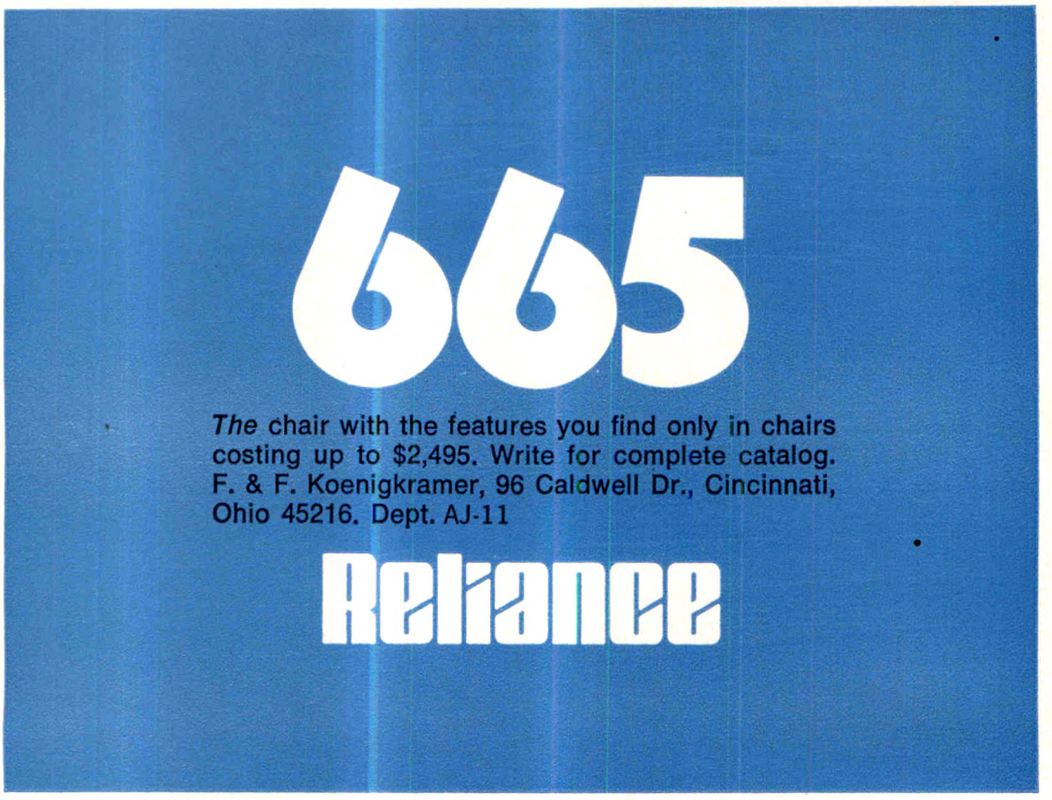
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Ref., Transactions American Academy of Ophthalmology and Otolaryngology, July-August 1970. Page 830

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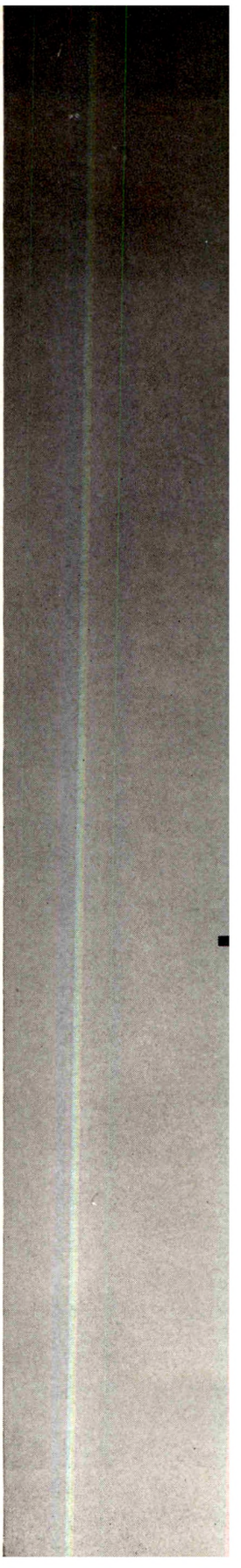
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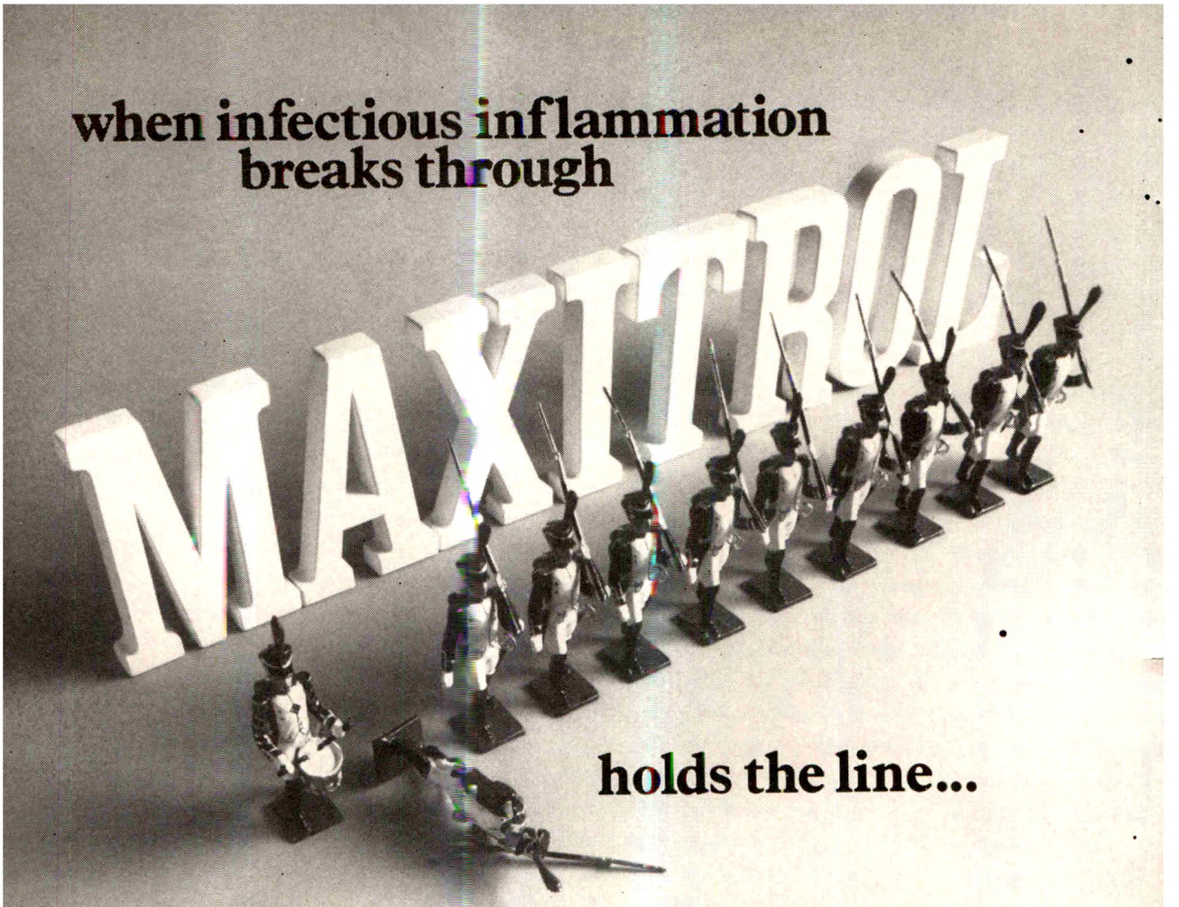
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References: 1. Nelson, E. L.: "Ophthalmic Steroids," in Kaufman, H. E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970. 2. Waltman, S. F. and Patrowicz, T. C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

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# REACTIONS FOLLOWING INTRAVENOUS FLUORESCEIN

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AND

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*St. Louis, Missouri*

Intravenous fluorescein is an important diagnostic and research tool in ophthalmology. The most common side effects have been nausea and vomiting. One manufacturer (Smith, Miller & Patch) warns physicians of no other adverse reactions. There are several reports[1-15] of more serious reactions, however, with some culminating in shock or cardiac arrest (Table 1). Toxic reactions have been reported,[15] and in addition, many reactions of an allergic type have been described. If these reactions were indeed allergic, identification of the responsible allergen would be important, as well as development of effective test procedures for the identification of susceptible individuals, as has been done in the case of penicillin allergy.[16]

This paper reports nine patients who sustained systemic reactions to intravenously administered fluorescein (Table 1). Intradermal skin testing for allergic reactivity was performed in the first three, using both sodium fluorescein 5% (Fluorescite) and fluorescein-conjugated human serum albumin (F-HSA). Hemagglutination and hemagglutination-inhibition studies were carried out on sera from these three patients in an attempt to demonstrate circulating antibodies to fluorescein. Additionally, hemagglutination studies were performed on the sera obtained before and after intravenous fluorescein administration from eight control patients.

From the Departments of Ophthalmology (Dr. Stein) and Medicine (Dr. Parker), Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by Public Health Service Research Grant EY-00336.

Reprint requests to Mervyn R. Stein, M.D., Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical Center, San Francisco, California 94122.

## CASE REPORTS

*Case* 1—This 61-year-old white woman had had multiple admissions for hypertension, atherosclerotic heart disease, atrial fibrillation, diabetes mellitus, and gout. She had a history of allergy to sulfonamides characterized by the development of urticaria. In 1964, an infranasal choroidal mass was discovered in the right eye. She was lost to follow-up until July, 1968, when the mass had enlarged to a size of 5-6 disk diameters. A fluorescein (Fluorescite) angiogram was attempted one month later. Ten ml (500 mg) of sodium fluorescein was injected into the antecubital vein. About 30 seconds later she became nauseated, then developed labored breathing with wheezing, followed by cyanosis and apnea. The femoral pulse was weak. An airway was inserted, and 0.5 ml of 1/1000 epinephrine was injected subcutaneously. Respiratory movements returned spontaneously; at first her breathing was shallow, and later it became deeper. The electrocardiogram revealed atrial fibrillation with multifocal premature ventricular contractions (PVC). The blood pressure stabilized at 220/120, and the PVC decreased in frequency. She was observed in the cardiac care unit for 48 hours and recovered uneventfully. The right eye was enucleated in April, 1969; pathologic diagnosis was malignant melanoma of the choroid.

*Case* 2—This 42-year-old black physician was seen in January, 1969, with central serous retinopathy in the left eye. He had a history of serum sickness following a tetanus antitoxin injection several years before, and he reported urticaria after the ingestion of oranges. There was a family history of

TABLE 1

SUMMARY OF CASES MANIFESTING REACTIONS TO INTRAVENOUS FLUORESCEIN

| Investigator or Institution Reported | Total No. Angiograms and Prevalence of Reactions | Case No., Age, and Sex | Ophthalmic Diagnosis | Allergic History | Description of Reaction | Prior Fluorescein Angiography | Remarks |
|---|---|---|---|---|---|---|---|
| Washington University School of Medicine (present report) | 1300 (0.69%) | 1. 51—F | Malignant choroidal melanoma | Sulfonamide | Wheezing, respiratory arrest | None | Hemagglutination study and skin tests negative; indirect Coombs procedure, 1:4 titer |
| | | 2. 42—M | Central serous retinopathy | Tetanus antitoxin, foods, familial asthma | Urticaria | None | Hemagglutination study and skin tests negative |
| | | 3. 43—M | Central serous retinopathy | Allergic rhinitis, penicillin (?) | Urticaria, facial edema | None | Positive skin reaction to F-HSA, 1:10 dilution; hemagglutination study negative |
| | | 4. 60—F | Serous detachment, macula | None | Pruritus, urticaria, hypotension | None | |
| | | 5. 24—F | Macular hemorrhage | None | Pruritus | None | |
| | | 6. 75—M | | None | Pruritus | | |
| | | 7. 62—F | Presumed histoplasmosis | Penicillin | Urticaria | None | |
| | | 8. 53—F | Optic atrophy | None | Urticaria | None | |
| | | 9. 50—M | Macular edema | | Dizziness, hypotension | | |
| Postgraduate Medical School of London[1] | 300 (0.33%) | 10. 61—F | Diabetic retinopathy | None | Loss of consciousness, bronchospasm, hypotension | None | Skin testing negative |
| University Hospital of Lund, Sweden[2] | 100 (1.0%) | 11. 28—M | | Allergic rhinitis, urticaria | Wheezing, dyspnea, urticaria, shock | None | Fluorescein exposure during desensitization procedure; skin testing negative |
| Amalric and associates[3] | 3000 (0.10%) | 12. 36—F | Metastatic choroidal tumor | | Loss of consciousness, apnea, seizure, hypotension | Once | |
| | | 13. | | | Fatal myocardial infarction | | |
| | | 14. | | | Urticaria | | |
| | | 15 | | | Edema of face and arms | | |
| Tohuku University of Japan[4] | 350 (1.14%) | 16. 47—F | Tuberculous retinitis (1945) | PAS (?) | Exanthema, shock | None | Prausnitz-Küstner test negative |
| | | 17–18. | | | Loss of consciousness | | |
| | | 19 | | | Urticaria | | |

TABLE 1 (*Continued*)

| Investigator or Institution Reported | Total No. Angiograms and Prevalence of Reactions | Case No., Age, and Sex | Ophthalmic Diagnosis | Allergic History | Description of Reaction | Prior Fluorescein Angiography | Remarks |
|---|---|---|---|---|---|---|---|
| Fairchild Air Force Base[5] | | 20. | | | Cardiac arrest | | |
| University of Chicago Hospitals[6] | | 21. | | | Cardiac arrest | | |
| | | 22. | | | Basilar artery ischemia | | |
| | | 23. | | | Shock | | |
| Palo Alto Medical Clinic[7] | 1600 (0.31%) | 24.–27. | | | Urticaria | | |
| | | 28. 39—M | Diabetic retinopathy | | Shock | None | |
| The Wilmer Institute[8,9] | | 29.–31. | | | Urticaria | | |
| | | 32. | | | Laryngeal edema | | |
| Walter Reed Army Hospital[10] | | 33. 30—M | Detachment of posterior vitreous face | Hay fever, foods | Pruritus, partial respiratory obstruction | None | Prausnitz-Küstner test negative |
| University Clinic for Venereal and Skin Diseases, Vienna, Austria[11] | 88 (1.13%) | 34. ?—F | | | Urticaria | | |
| Bascom Palmer Eye Institute[12,15] | 1000 (0.2%) | 35.–36. | | | Urticaria | None | |
| | | 37.–42. | | | Pyrexia | | Probable contamination in Fluorescite |
| University of California Medical Center at San Francisco[18] | 2490 (0.48%) | 43.–52. | | | Urticaria | | |
| | | 53. 73—M | Serous detachment, macula | Codeine (?) | Urticaria | None | |
| | | 54. 73—M | Serous detachment, macula | Codeine (?) | Urticaria | Two months earlier | |
| Ohio State University[14] | | 55. 36—M | None | Penicillin, hay fever | Urticaria, edema of face and hands | None | |

asthma. His general health was otherwise unremarkable. A diagnostic fluorescein (Fluorescite) angiogram was performed. Sixty seconds after a 10 ml injection he became nauseated. His vital signs were within normal limits, and his lungs remained clear, but in another 60 seconds, transient urticaria appeared on the left thigh.

*Case* 3—This was a 43-year-old exiled Cuban physician, referred to Dr. Alan Kolker because of central serous retinopathy. At the time of his examination (April 15, 1969), he was taking a corticosteroid (Prednisone) in a dosage of 40 mg daily. He had had allergic rhinitis during the previous year. A papillary reaction occurred on the tongue following penicillin therapy. The patient developed generalized urticaria with facial edema within five minutes of the intravenous injection of 10 ml of sodium fluorescein (Fluorescite). There was no laryngeal edema. The urticaria quickly subsided.

In addition to these cases of drug reactions to intravenous fluorescein, there were two cases of pruritus, two cases of urticaria, one case of urticaria with hypotension, and one case of dizziness with hypotension seen at Washington University School of Medicine in the period of January, 1968, to June, 1971.

## Experimental procedures

*Skin testing*—Skin testing was performed

in two steps, using sodium fluorescein (Fluorescite) and F-HSA at a maximal concentration of 7.7 mg/ml. The latter was obtained by conjugating fluorescein isothiocyanate with human serum albumin in a bicarbonate buffer and purifying the material by prolonged dialysis.[17] The extent of the conjugation was determined with a spectrophotometer on the basis of absorbance at 280 and 490 mμ. It was estimated that there was an average of 13 fluorescein groups per molecule of albumin.

The patients were scratch-tested with 1:100 and 1:10 dilutions of sodium fluorescein and F-HSA. Since the scratch tests were negative at both concentrations in the three patients tested, intradermal injections were employed. The first two patients were skin tested by the authors. The third patient (a physician) was unable to return so the solutions were sent to him and he was skin-tested by a medical colleague. He was no longer taking systemic corticosteroids at the time of skin testing. The skin test solutions were tested in normal subjects for their ability to produce nonspecific irritation, and there were no reactions at any concentration.

*Human sera sources*—Blood was obtained from all three patients who had experienced the drug reactions; in the first patient, it was taken one month later, in the second, it was taken two days afterward, and in the third, two months after the reaction. A control group of eight patients undergoing fluorescein angiography was also studied. There were five with diabetic retinopathy, one with pseudoxanthoma elasticum, one with macular degeneration, and one with retinal detachment. Blood specimens were obtained prior to and 10 to 14 days after the fluorescein study. A nonspecific control serum was collected from a laboratory technician.

*Rabbit sera*—New Zealand rabbits were immunized with one mg of F-HSA in complete Freund's adjuvant injected into the footpads, and serum was obtained four to six weeks later. On the basis of quantitative precipitin analysis, the serum was found to contain 200 μg/ml of antibody. Rabbit antiserum to human gamma globulin was obtained by the method of Thiel and associates.[16]

*Hemagglutination technique*—A modification of the technique employed by Thiel and associates[16] for the detection of hemagglutinating antibodies to penicillin and its derivatives was used. In this procedure fluorescein isothiocyanate is covalently bound to human red blood cells and the cells are agglutinated by sera containing anti-fluorescein antibodies.

Sensitization of human red blood cells with fluorescein was accomplished in the following manner. Washed Group O, Rh-negative human red blood cells were obtained from a single donor and mixed with an equal volume of Alsever's solution. The cells were washed three times with a solution containing 0.15 M NaCl, 0.008 M $K_2HPO_4$ and 0.002 M Na $H_2PO_4$,pH 7.4 (phosphate-saline). An equal volume of 0.15 M NaCl solution was then added to the packed red blood cell volume to produce a 50% suspension. One volume of the suspension was added to a solution containing 30 volumes of a 0.15 N sodium barbital buffer, pH 9.8, and 0.3 volume of a suspension of fluorescein isothiocyanate in acetone containing 5 mg/ml. The resulting mixture was incubated for one hour at 37°C, washed three times with a wash solution (20.5 g dextrose, 20 g EDTA disodium salt, and 4.2 g NaCl in one liter of distilled water, with 2 g of bovine serum albumin added just before use) and the blood cells were finally diluted to a 1% suspension in this medium.

Serial four-fold dilutions (from 1:4 to 1:256) of human and rabbit sera were made up in duplicate using phosphate-saline. Half of the tubes received $2.5 \times 10^{-4}$ M sodium fluorecein in phosphate-saline. An equal volume of the 1% fluorescein-treated red blood cell suspension was added to all the tubes. They were shaken thoroughly and then examined for hemagglutination and hemagglutination inhibition at 30 and 90 minutes. An identical set of tubes was made up and used in carrying out a subsequent indirect Coombs test.

A 2-plus hemagglutination reaction[18] was consistently obtained in this experiment with rabbit anti-fluorescein sera at the 1:256 dilution. Furthermore, the reaction was consistently inhibited by unbound sodium fluorescein at a concentration of $10^{-3}$ or less. Fluorescein-treated red blood cells incubated with phosphate-saline alone did not agglutinate.

*Indirect Coombs procedure*—The Coombs procedure was employed to accentuate the hemagglutination response. Rabbit anti-human gamma globulin was absorbed with the cells preincubated with sera, and observed for agglutination at 30 and 90 minutes.

## Results

*Skin testing*—The scratch tests were negative to both sodium fluorescein and F-HSA at both the 1:10 and 1:100 dilutions in all three patients. The third patient had a positive intradermal response to F-HSA at the 1:10 dilution, but showed no reaction to sodium fluorescein. Unfortunately, we did not conduct, nor did we witness the skin testing, and the role of albumin in the skin reaction was not elucidated. Therefore, the signifiance of this positive result is questionable. The other two patients had negative intradermal reactions.

*Hemagglutination reaction*—The sera from the three patients who manifested idiosyncratic reactions to intravenous fluorescein, as well as the sera obtained before and after fluorescein injection in eight control patients, produced negative hemagglution reactions. The nonspecific control serum was weakly positive at the 1:4 dilution, and its reaction with antigen-coated red cells was inhibited by sodium fluorescein.

Testing with the Coombs reagent produced a weakly reactive response at the 1:4 dilution in the pre-angiographic serum of one of the control patients with diabetic retinopathy, but was negative in the post angiographic serum from the same patient. Among the three patients being studied, the first had a moderate reaction at the 1:4 dilution. Both responses were inhibited by sodium fluorescein. Frequently, false-positive results are obtained with the hemagglutination test at the lowest titer (i.e., 1:4). Therefore, we cannot place a great deal of confidence in these elevations, especially since the nonspecific control had a 1:4 titer.

## Discussion

We have collected 55 cases of reactions to intravenous fluorescein in 54 patients (Table 1), including several of our own cases.[1-15] The majority of the reactions (67.3%) were of an allergic type (Table 2), and most of these were characterized only by urticaria. About 29% (16) of the reactions were of a severe nature, and 11 presented a shock-like picture. Seven of the 16 severe reactions appeared to be allergic in type and these consisted of two cases of shock, two cases of respiratory obstruction, a case of respiratory arrest, a case of hypotension, and a case of hypotension with loss of consciousness. Cardiac arrest, shock, loss of consciousness and myocardial infarction were the main diagnoses in the non-allergic group. In most cases, recovery was uneventful, but one patient developed a myocardial infarction several hours after the procedure and died.[3] Of the cases in which the sex was stated, half were male. The age range was from 24 to 75 years with a mean of 48.2 years.

For each institution, the prevalence rate was calculated from the total number of reactions versus the number of fluorescein studies, where this information could be obtained. It varied from 0.1 to 1.14%. The prevalence rate for severe reactions was even lower, ranging from 0.06% to 1.00%. We cannot be sure whether the differences between institutions were significant, as the number of drug reactions and angiographic studies in some series were small. Nevertheless, with this limitation in mind, the mean rate for all types of reactions in this review was 0.60% (six reactions per 1000 angiographic studies performed) and for severe reactions it was 0.41% (four reactions per 1000 angiographic studies performed). This incidence is worthy of consideration, especially for institutions performing large number of studies. In

TABLE 2

TYPES OF REACTIONS FOLLLOWING INTRAVENOUS ADMINISTRATION OF FLUORESCEIN

| Degree | Allergic Type | Non-allergic Type |
|---|---|---|
| Mild | 30 | 9 |
| Severe | 7 | 9 |
| Total | 37 | 18 |

the light of the seriousness of some of the reactions, as well as the sporadic nature of their occurrence, certain safety precautions should be taken. It would seem desirable to perform the study in a room large enough to allow for comfortable treatment of the patient.[3] Administration of the fluorescein through a small indwelling catheter[3] has value, since the vein can be kept open in the event that a severe reaction should develop. An emergency tray should be available.[3,4,10] It should contain epinephrine HCl solution 1:1000, diphenylhydramine HCl (Benadryl) parenteral, aminophylline, metaraminal bitartrate (Aramine), hydrocortisone sodium succinate (Solu-Cortef), parenteral fluid with intravenous adapters, syringes, needles, an airway, and oxygen.[19,20] Finally, one should be prepared to act in a rapid and efficient manner, with maximum utilization of ancillary staff.

Drug allergies of the immediate hypersensitivity type are thought to be the result of an immunologic response of the host to a hapten (drug)-protein combination. Nearly all drugs attach themselves by reversible bonds to proteins, especially albumin, but this combination does not appear to be antigenic. Apparently antigenicity is determined by the ability of the drug to produce a stable or covalent bond with the protein.[21,22]

In the case of many drugs, the allergic reaction is probably the result of the conjugation of serum protein with degradation products of the drug. Support for this concept is provided by experiments on penicillin allergy. Several penicillin derivatives, notably the penicilloyl group,[16] have been found to be the important antigenic determinants. These derivatives conjugate covalently with protein; however, penicillin and several other derivatives, which are poor sensitizers, are bound reversibly to serum albumin.[21]

Fluorescein, when injected intravenously, is adsorbed in large part (50-84%) to plasma proteins (mainly the albumin fraction),[23] and also to red blood cells (15-17%).[24] The resulting bond is weak.[25,26] Webb and associates[27] have shown through paper chromatography studies in rats that fluorescein is not degraded in animal tissues, but is excreted mainly in the urine, unchanged, and partly by way of the liver after conjugation with glucuronide. It is also rapidly excreted in the urine in man.[28]

Do these drug reactions have an immunologic basis, and, if so, is fluorescein the responsible allergen? Since fluorescein does not bind covalently to the plasma proteins it would not appear to be an important sensitizer, and this is supported by the available experimental results. Antibodies to fluorescein were not conclusively demonstrated in any of our own or our collected cases. One of our three patients (Case 3) manifested a positive intradermal test to F-HSA at a 1:10 dilution. This may have been an immunologic reaction to conjugated fluorescein, but we did not perform the test, nor did we observe the reaction. Furthermore, testing with albumin would have been useful to strengthen the case for allergy to fluorescein itself. The Prausnitz-Küstner test was performed in two reported cases,[4,10] and skin testing was employed in two others.[1,2] All results were negative. In addition, we were unable to demonstrate the development of circulating antibodies to fluorescein by the hemagglutination technique in the eight control patients, or in the three cases of drug reactions. The argument that the fluorescein-tagged red blood cells were insufficiently sensitized with fluorescein does not seem valid, since rabbit antisera to fluorescein at high dilutions gave strongly positive agglutination reactions. Although Case 1 and one of the control patients had positive responses at the 1:4 dilution in

the indirect Coombs test, the significance of a 1:4 titer is questionable. Insofar as fluorescein has not been found to be degraded metabolically,[27] the formation of small quantities of breakdown products has not been excluded, and these could act as sensitizers.

It is possible that the inciting haptene was a contaminant. According to their weekly recall list (May 8, 1970), metallic and ionic mercury have been detected in fluorescein vials by the Food and Drug Administration. Mercury has resulted in hypersensitivity reactions.[29] However, it cannot be implicated as the primary cause of these allergic reactions, since several cases of urticaria were noted subsequent to the second release of the mercury-free fluorescein.[7,13]

Finally, the reactions may have been caused by nonallergic mechanisms. A vasovagal type response is a distinct possibility in several cases (i.e., Case 9). Since many drugs cause histamine release in vitro in the absence of an antigen-antibody reaction,[30] histamine should be considered as a possible causal factor. There is little evidence, however, that drug reactions of the type described in this review are mediated by this pathway. An embolic effect from the rapid injection of a bolus of dye, with transient ischemia of vital organs, must be raised as a possible mechanism. Several cases appear to be the result of a direct toxic effect—a probable contaminant resulted in a series of pyrexic reactions at the Bascom Palmer Eye Institute.[15] Inorganic mercury can result in an acute toxic reaction,[31] however, the concentration of mercury administered in the cases cited in this study was probably too low to be toxic.

If some of these reactions were due to an allergy to fluorescein, how were these patients sensitized? The topical route would be a likely source of sensitization, as many of the patients in this review had received topical fluorescein previously. However, Theodore and Schlossman[32] state that topical fluorescein "is rarely, if ever, a sensitizer." Sensitization from a previous intravenous injection might be considered, but we uncovered only two cases in which previous angiographic studies had been performed. One patient had a reaction to the second, but not to the first injection;[3] in the other patient, urticarial reactions occurred after both studies.[13] If the intravenous route is an important pathway for sensitization, the incidence of adverse reactions might be expected to increase as more and more patients are exposed to repeat angiograms. Sensitization by another route is possible since fluorescein is a widely distributed substance in our environment.

Since there is an increased risk of drug allergies in atopic individuals,[33] it is important to probe for a history of allergy where this is possible. A positive history was obtained in seven of 14 cases where it was specifically sought, and in three of these there was a history of drug allergy. In three other cases, a history of a drug reaction was obtained, but it was not typically allergic in nature. We have no information regarding allergy among the other cases depicted in Table 1.

## Summary

Nine cases of reactions following intravenously administered fluorescein are reported with a review of the literature. Skin testing was performed in three of the nine patients, using commercial fluorescein and fluorescein isothiocyanate conjugated with human serum albumin (F-HSA). A positive response to F-HSA at the 1:10 concentration occurred in one of them, but the reaction was not witnessed by the authors. Hemagglutination and hemagglutination inhibition studies were conducted on sera from these three patients and from eight control subjects who had undergone fluorescein angiography. Significant antibody levels to fluorescein could not be detected in patients or controls. Reactions to intravenous fluorescein are reported to occur in 0.6% of patients undergoing angiography. The majority of the reactions were of an allergic type (67.3%), but a significant percent (29.1%) were severe in na-

ture. Therefore, an emergency tray and oxygen should be readily available when angiography is performed. The possible mechanisms underlying these reactions are multiple.

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# JOHANNES KEPLER ON THE EYE AND VISION

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This year the scientific world celebrates the quadricentennial birthday of Johannes Kepler (Fig. 1), and it appears fitting on this occasion to touch on some aspects of his work concerning ophthalmology. It seemed desirable on two accounts:

1. The pertinent Latin books are not available in English, and only fragments have been translated into German. This inaccessibility of original sources may explain errors published repeatedly by various authors. It is hence a purpose of this communication to present Kepler's views as he himself stated them.

2. The short comments on these views are aimed at providing a degree of perspective. Studying the work of great scientists of the past affords insight into the general art of scientific investigation.[1] It serves to remind us that the intellectual effort required for scientific progress has not been changed or lessened by the more sophisticated tools available today. The ontogenesis of each individual scientist historically follows the phylogenesis of science at large.

Concerning ourselves with ophthalmology alone hampers a complete portrayal of Kepler's genius. He is best known for his three laws of planetary motion which paved the road to Newton's celestial mechanics and modern space trips. His elucidation of refraction through lenses—the Dioptrice—ranks second only to Euclid's classical Catoptrics. In this field, Kepler explained the workings of Galileo's terrestrial telescope and proposed the astronomical one, also known as the Keplerian telescope, variations of which were incorporated into numerous other optical instruments such as the microscope. His work in astronomy and optics required a good deal of mathematical knowledge; in this area, too, Kepler added new knowledge on logarithms and infinitesimals.

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## SOURCES

The material of ophthalmic interest is contained in two books. The first, commonly referred to as *ad Vitellionem,* or *Astronomiae pars optica* (Fig. 2), was published in 1604, and its title translates: *Supplements to Witelo, in connection with the optical part of astronomy, especially on the proper observations and estimations of the waning diameters of the sun and moon, with examples of significant eclipses. In this book the reader is offered, among many other new subjects, a most lucid treatise on the mode of vision, and the use of the ocular humors, contrary to views held by opticians and anatomists.*

The second and much shorter book (Fig. 3) was published in 1611, and essentially complements and supplements the first. Its

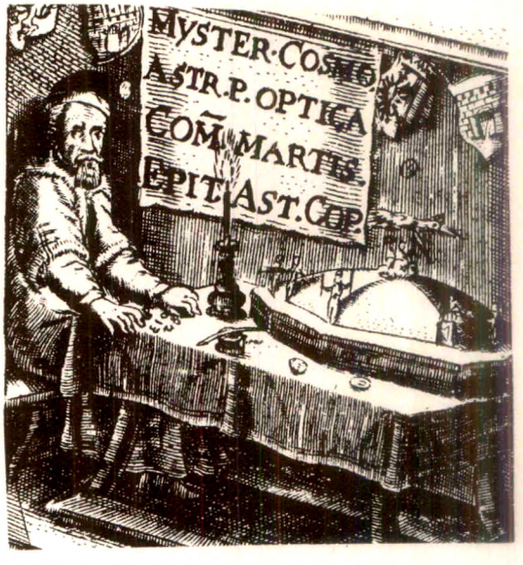



Fig. 1 (Mark). Kepler at work, with abbreviated titles of some of his books. From the title page of his *Rudolphine Tables,* 1627.

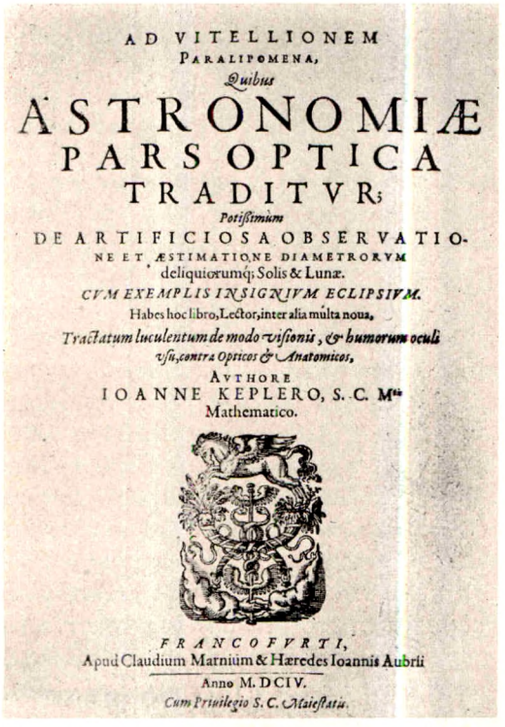

AD VITELLIONEM
PARALIPOMENA,
Quibus
ASTRONOMIÆ
PARS OPTICA
TRADITVR:
Potiſſimùm
DE ARTIFICIOSA OBSERVATIONE ET ÆSTIMATIONE DIAMETRORVM deliquiorumq; Solis & Lunæ.
CVM EXEMPLIS INSIGNIVM ECLIPSIVM.
Habes hoc libro, Lector, inter alia multa noua,
Tractatum luculentum de modo viſionis, & humorum oculi viſu, contra Opticos & Anatomicos,
AVTHORE
IOANNE KEPLERO, S. C. Mtis
Mathematico.
FRANCOFVRTI,
Apud Claudium Marnium & Hæredes Ioannis Aubrii
Anno M. DCIV.
Cum Priuilegio S. C. Maieſtatis.

Fig. 2 (Mark). Title page of Kepler's main book on vision, 1604.

full title translates: *Dioptrics, or, demonstration of the effects which the newly invented telescope has on vision and the visible.* In this second book, Kepler's theory of accommodation is of particular interest to us.

## Anatomy

Kepler's main endeavor is in astronomy, but, as he says, "astronomical observations depend ultimately on the human eye. Therefore, in order to avoid inaccuracies and deceptions, it is necessary to study the eye, and to begin with its anatomy." Since, however, Kepler had no first-hand knowledge of the subject, he accepted "the torch from authorities in anatomy in order to illuminate with it the physical problems."

The anatomy of the eye depicted in Figure 4 was drawn by Kepler mainly from Felix Palter,[2] in conjunction with works of John Jessen[3] and Fabricius ab Aquapendente.[4] Figure 4 conforms accurately to the eye depicted in Vesalius' *Fabrica,*[5] and is not far removed from ancient Galenic concepts.

## Kepler's concepts

*The orbit*—This is the bony shield of the eye. The eye protrudes out somewhat in order to attain a wider visual field. The orbital axes are directed downwards and temporally to facilitate social intercourse and also to see better the feet and mouth, needed for locomotion and nourishment. To this end, too, the face between the nose and the cheek is depressed. The forehead protrudes above the eyes to shield them from overhead lights.

The nose between the orbits forms a dam to prevent one eye from seeing the other, which would impair vision by reflections. That part of vision, however, which is thus obscured for one eye, is complemented by the other, for with two eyes Nature achieved complete vision.

*The eyelids*—These protect the eyes by keeping them moist and by wiping off foreign matter and discharge. In order to function properly as occluders and wipers they

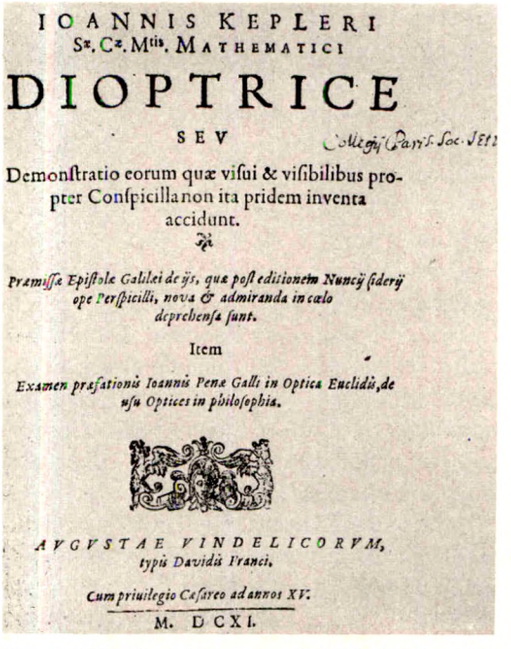

IOANNIS KEPLERI
Sæ. Cæ. Mtis. MATHEMATICI
DIOPTRICE
SEV
Demonſtratio eorum quæ viſui & viſibilibus propter Conſpicilla non ita pridem inventa accidunt.
Præmiſſa Epiſtole Galilei de ijs, quæ poſt editionem Nuncij ſiderij ope Perſpicilli, noua & admiranda in cælo deprehenſa ſunt.
Item
Examen præfationis Ioannis Penæ Galli in Optica Euclidis, de uſu Optices in philoſophia.
AVGVSTAE VINDELICORVM,
typis Dauidis Franci.
Cum priuilegio Cæſareo ad annos XV.
M. DCXI.

Fig. 3 (Mark). Title page of Kepler's Dioptrics, 1611.

must remain in contact with the globe in all positions and with their entire surface; this can be achieved only by hemispherical shutters anchored on each side of a sphere, as the eyelids are. The eye brows and lashes shield the eye from excessive light and from foreign bodies. Upon blinking, the lashes also work as fans, blowing approaching dust away.

*The globe*—This has a spherical form for easy rotation on all axes, essential for complete vision. The center of rotation is also the center of the sclera, uvea, and retina. The lens is slightly in front of this center.

The globe resembles an onion with its stalk in the brain. The hard membrane of the brain forms the sclera and cornea, the soft membrane of the brain forms the sclera and cornea, the soft membrane forms the choroid posteriorly and the uvea anteriorly, and the brain itself forms the optic nerve and retina.

*The conjunctiva*—This springs from the periosteum of the orbital rim. It contains nutritive vessels and also helps retain the globe in the orbit.

*The cornea*—The cornea is avascular. Its radius of curvature is smaller than that of the sclera, and indeed may not be spherical at all but rather spheroidal in order to counteract spherical aberrations.

*The sclera*—This is white in order to reflect light away, for its absorption by a dark color would generate injurious heat.

*The iris*—This is variously colored to accentuate it from the white sclera and black pupil. In this manner, we can tell immediately when someone is looking at us. The stiff and smooth body of the iris occasionally emits sparks by internal friction, similar to those produced by stroking a cat or freshly cut hair.

*The pupil*—The pupil dilates in the dark up to three times its normal size in order to admit more light to the lens. It constricts in bright light and on looking at near objects.

*The choroid*—This is half as thick as the iris, and is attached to the sclera by fibers.

*The ciliary processes*—These originate in the uvea (not in the retina) and are anchored to the lens, which they nourish. With the lens they form a septum between the aqueous and vitreous humors. The processes are all black, swell in bright light, and shrink in the dark. The purpose of the whole uvea is to provide darkness inside the eye.

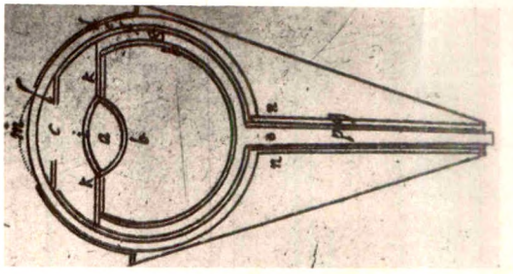


Fig. 4 (Mark). The human eye.

*The aqueous humor*—This is in direct contact with the cornea, iris, lens, hyaloid, and ciliary processes. It has no membrane. Its function is to fill the chambers and to maintain a uniform refractive index between the cornea and lens.

*The crystalline lens*—This is located only a little in front of the center of the globe. It is encapsulated by a membrane to prevent penetration of aqueous humor. The crystalline is an optical lens with a spherical, convex front surface parallel to the corneal surface, and a hyperbolic posterior surface. As a biconvex lens, it reduces and inverts the image of a distant object when the receptive screen is farther behind the lens than the length of its radius.

*The vitreous humor*—This is covered by the hyaloid membrane which separates it from the aqueous humor and the retina. Its refractive index is lower than that of the lens, for otherwise light would not emerge convergent from the lens. The vitreous holds the retina taut against the uvea.

*The retina*—This originates in the optic nerve and spreads forward to end in front of the ciliary processes. Its form is thus larger than the hemisphere and correspondingly, our visual field is wider than 180°. Kepler states: "That this is so I have proven to my-

self, for I often saw the sun and my shadow simultaneously; one does not miss by much to see one's own ears, particularly if they are large."

*The optic nerve*—This is located diametrically opposite the pupil and lens, and is therefore the site of best vision. It possesses a twisted channel connected to the brain. No optical image can be transmitted through the nerve, only the visual impressions from the retina. The two nerves unite and cross in order to connect the brain equally to both eyes; when one side of the brain or nerve is damaged, the eye will thus maintain its contact with the sensorial centers. The nerves do not cross in order to see singly with both eyes, for we can see double even with intact nerves.

## Comment

Kepler's anatomy of the eye bears heavily on his physiological optics. In general, we note his then common teleologic approach which assigned to structure an ulterior purpose. This intimate association sounds naive today, but is still held subconsciously at present, for one always tacitly assumes that any structure has a purpose, or, as von Bruecke put it, "teleology is a lady without whom no biologist can live; yet he is ashamed to show himself in public with her."

Kepler himself occasionally expressed conflicting teleologic views. At one point, for instance, he asserts that two eyes were not made in order to protect vision in case one is lost "for Nature designs nothing against loss"; at another point he explains that the purpose of the two optic tracts is to preserve vision in case one is damaged. Today we may simply accept two eyes as a fact, and then proceed to study the advantage of the situation extant. One wishing to explain why we have two eyes would look to the evolutionary development of symmetry in living organisms, rather than extrapolate their existence from the advantages of their function.

The structure of the crystalline lens was theoretically deduced by Kepler from its function. Since spherical lenses cause optical aberrations detrimental to a clear image on the retina, the lens (and cornea) had to be given a spheroidal shape. Similarly, the refractive index of the vitreous had to be higher than that of the lens to accommodate Kepler's theory which called for light from the lens to converge on the retina. Such deductions are commonplace in mathematics and physics, but may have dubious value in biology. Kepler's reasoning is thus amazing in its proximity to the actual facts as we now know them.

On the other hand, Kepler's visual theory suffered because of inaccurate anatomical data. Chief among them was the central position of the lens in the vitreous cavity. This location was assigned to it in antiquity, was formalized by Galen, and this belief continued until the 18th century when cataract extractions began. Fabricius ab Aquapendente correctly placed the lens right behind the pupil, but the idea did not prevail, so that, for instance, a notable anatomist and ocular surgeon such as William Cheselden in the 18th century wrote of the large space between the pupil and lens.

Interesting also is the description of the aqueous humor in direct contact with its surrounding tissues. A capsule containing the humor has been described as late as the 19th century, and a disease, aquocapsulitis, was then assigned to it.[6] Evidently even in anatomy newer knowledge is not necessarily tantamount to enlightenment.

## Vision

"I shall describe the process of vision as never before explained or comprehended to the same degree," Kepler states. "Vision ensues when the entire external hemisphere, and somewhat more, is brought into the concave surface of the retina. How this image on the retina becomes conscious to the soul I shall leave for others to explain."

He continues: "Each single point of the external object forms the apex to a cone of light which has its base on the anterior sur-

face of the crystalline lens. To this cone corresponds another one with the same base but with an apex on the retina. The anterior cone is somewhat refacted by the cornea, the posterior one by the posterior face of the lens. All cones from all points intersect at the pupil on their way to the lens. The divergent rays from the objective point become convergent by refraction at the cornea. Therefore, the larger circle of light formed on the cornea shrinks to fit the smaller aperture of the iris, and is still smaller when it reaches the lens. No refraction occurs on the anterior surface of the lens because the refracted rays from the cornea fall perpendicular to it. The rays do, however, become more convergent by refraction at the hyperbolic surface of the posterior lens, and they finally unite exactly at the center of the optic nerve head. Best vision is attained when all the rays from one objective point passing through the pupil are reunited after two refractions (at the cornea and posterior lens) at one point on the retina (Fig. 5).

"Another point of the object, to the right of the central one, will send an oblique cone of light to the pupil. It will cross the first cone at the pupil and will land upon the face of the lens to the left of the first one, similar to what happens in a camera obscura. The crystalline lens in the eye represents the posterior wall of the camera. Behind the lens no rays intersect; therefore, an object located between the pupil and the lens will appear inverted (Fig. 6). The image on the lens is still blurred because not all rays have yet intersected; only after refraction by the lens

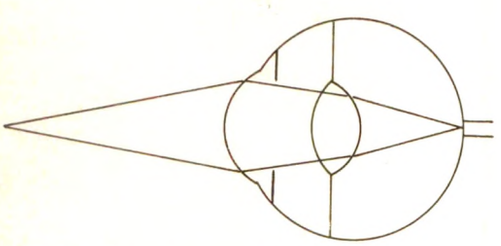


Fig. 5 (Mark). The course of light from a point-object through the eye (after Kepler's text).

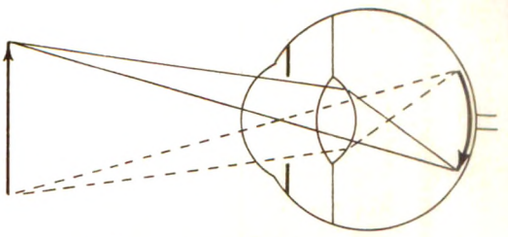


Fig. 6 (Mark). Image formed in the eye by an extended object (after Kepler's text).

do all rays unite perfectly on a point on the retina.

"According to optical principles, which I have elsewhere sufficiently proven by several demonstrations, the image on the retina is inverted in relation to the external object. To those who object, I say that vision is not an action, though illumination is one. Vision is a passive impression—a reaction to the action of light. Besides, the inverted image is still completely proportional in the relative position of its details. The eye also knows its own position, and when it sees something high it spontaneously turns upwards.

Rays from lateral points of the objects form oblique cones on the way to the eye. They are therefore refracted not only by the cornea and posterior lens face but also by the anterior lens. Furthermore, the entry pupil now is vertically oval. All this causes these rays to form an indistinct image on the retina. The retina itself has only a weak sensorial power at these peripheral areas. Hence peripheral vision does not satisfy the eye but merely invites it to turn toward it to form direct and distinct vision. The peripheral images flow as in a funnel toward the optic nerve, and contribute to the formation of a complete picture.

*Spherical aberration*—"Rays incident on a spherical lens at its periphery are more refracted than those which pass it centrally; in a convex lens they converge to a focus nearer the lens. In the eye this phenomenon is counteracted in three ways: First, the pupil excludes the peripheral parts of the crystalline lens. Second, the posterior face of this

lens is aspherical, and, finally, the peripheral parts of the retina are closer to the lens than the central parts. The image on the retina remains sharp even when the pupil is dilated since the other two factors are still operative.

"Very near objects always appear blurred because the focal point of their rays recedes into the head, leaving on the retina a diffuse circle instead of a sharp point.

*Physiologic diplopia*—"When both retinas are similarly affected, we see singly; when dissimilarly affected, we see two pictures of the same object. In Figure 7, the eyes (Band C) are looking at an object (F). Point D is projected on the retina of eye B at a different place from point F, whereas in eye C both points project to the same place. Therefore, point D appears double.

*After-imagery*—"Vision is a sensual perception by the brain of the stimulated retina. The visual spirits are either offered to the brain by the retina, or else the brain requests the information from the retina. Light and colors cause a change within the structure of the retina rather than merely paint a picture on it; this is analogous to the burning of paper by means of light concentrated upon it. The change in the retina is not contemporaneous with the stimulus, for the image may remain after the stimulus had subsided.

*Depth perception*—"Distant objects as well as small ones subtend a small angle at the eye—near or large ones, a larger angle. The distance of an object from the eye may be judged best by the use of both eyes, since these are separated from one another by a certain distance. As long as there is a noticeable ratio between the interocular distance and the distance of the viewed object, the latter distance may be perceived.

"A single eye may also judge distances by being moved from one vantage point to another. This in effect creates vision from two separate angles similar to simultaneous vision with the two eyes. Furthermore, the eye is capable of sensing the degree of refraction in its media and the degree of diminution in the intensity of light passing through its humors, and in this manner judge the distance of the object from which the light emanates.

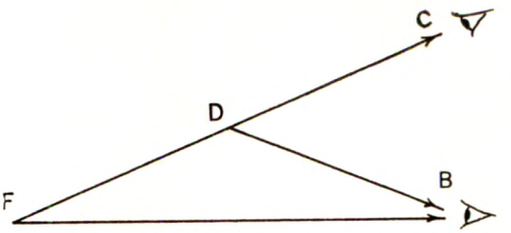



Fig. 7 (Mark). Physiological diplopia explained.

*Inhibition*—"Of objects of equal size, those which are brighter appear larger, and the less luminous ones appear smaller. A brightly illuminated area of the retina inhibits clear vision in the neighboring areas."

## Comment

Prior to Kepler, the commonly accepted theory of vision saw the lens as the perceptive organ. The notion originated with the ancient Greeks and was taken over by Alhazen in his book on optics. The book was written in Arabic in the 10th century and was translated into Latin by Witelo in the 13th. Even such a notable optical luminary and contemporary of Kepler as John Baptista Porta[7] accepted it.

Toward the end of the 16th century, a few observers noted that the crystalline lens, when removed from the eye, acted as any other optical lens. Among them was the obscure Franciscus Maurolycus[8] and the more widely known Felix Plater.[2] Lacking insight into physical optics, they understood the action of the crystalline lens to be one of mere magnification.

It was thus Kepler's brilliant accomplishment to confirm that the lens was indeed an optical instrument, and as such he documented its action within the eye. He did this by applying to the eye his thorough knowledge of physical optics in general and of lenses in particular. So convincing was his demonstration that the revolutionary idea of the inverted retinal image was accepted in the bargain. The experimental proof was

furnished by Christopher Scheiner a few years later.

Reducing the function of the eye to clearly comprehensible physical events had both immediate and delayed consequences. Once the veil of mystery had been lifted from the act of vision, man needed no more stand in awe of it. It became unnecessary to worry whether the images seen through spectacles and telescopes were real or merely a demoniac deception brought about by these heretic devices. It was sometimes argued that if God wanted man to see more, He would have given him the necessary eyes. But when Kepler showed that the eye functioned along the same lines as the artificial optical tools, the whole problem evaporated into thin air.

Similarly, once it had been understood how the crystalline lens functions, its removal could be contemplated in more rational terms. The first obstacle to cataract extraction was thus overcome. All that was lacking in Kepler's time was the proof that cataract was indeed an opacity of the lens. This proof came 100 years later.

The camera obscura, a name Kepler coined, was known since antiquity and commonly used in astronomy. This knowledge, together with the superficial resemblance of the eye to such a camera, must have prejudiced Kepler. He thus made incidental light intersect at the pupil in front of the lens, asigning the latter a secondary role—a role dictated perhaps also by the deep position of the lens within the globe.

On the other hand, his conflicting views concerning the dioptrics of the eye are biased in favor of the newly discovered lens. At one time he stated that the cone of light from the object is based at the lens; another time he stated its base to be the cornea, from which it converges onto the lens.

Today we know, of course, that the eye is mainly a dioptric apparatus which, contrary to a camera obscura, may still function without an iris diaphragm. Its nodal point (or points) is in the posterior part of the lens or behind it, the cornea being the main refracting surface. But all this is founded on what Kepler began, and came to us refined through the able minds of C. F. Gauss and H. L. Helmholtz in the last century.

Kepler's idea that the curvatures of the cornea and anterior lens were identical was taken from Alhazen. The latter required the concept since he believed that light was lost by refraction, and hence could not be accurately perceived. To Kepler's theory of vision it was irrelevant.

Among the many novel ideas expressed by Kepler we note: (1) The correspondence of the visual field to the area of the retina. (2) The varying visual angles at which objects of different size or distance subtend at the eye. (3) The inverted and reduced retinal image. (4) The proprioceptive consciousness of the position of the globe in space. (5) The difference between central and peripheral vision. (6) Inhibition processes within the retina. (7) Corresponding retinal points as prerequisite to single binocular vision. (8) The ability of the eye to sense the degree of refraction occurring in its media. This last idea is similar to his notion that a free-floating image may be perceived by the onlooking eye.

Of lasting value remain Kepler's elucidation of the refractive errors and of accommodation, which follow directly from his visual theory, based upon available anatomical and optical data.

## Refractive errors

Kepler states, "Those who see clearly at distance but indistinctly at near are helped by convex spectacles, and those who see poorly at distance but well at near are helped by concave spectacles. How amazing that while the practical use of this fact is so widespread, its scientific cause remained obscured.

"I myself believed, with Porta and others, that convex lenses help vision because they magnify. They do so indeed for all eyes, but render the object more distinct only for those who see well at distance. Similarly,

concave lenses reduce a distant object for all, but clarify it only for those who see it clearly at near; for those who see clearly at distance these lense may indeed blur the object.

"For those who see well only at distance, convex lenses modify the cone of light emanating from a near object to appear as if it arrived at the eye from distance—that is, parallel. The light is thus focused on the retina, and the near object is well perceived. Without these lenses, all light from a near object unites behind the retina, and upon it remains merely a blurred image by the overlapping circles.

"For those who see well at the near, the concave lenses modify the light from a distant object to appear as if it arrived from near (Fig. 8), and thus the object is well perceived. Without these lenses, the light from a distant object will unite before reaching the retina, and when it reaches it, will again be wider and confused. This I found confirmed by experience: I know two gentlemen of nobility one of whom can read the smallest print, but at such close distance that he cannot use both eyes together. With deeply concave lenses he sees perfectly well at distance, but these same lenses blur the distance pictur for me although I wear lenses that are concave—but weaker. Each myopic person needs his specific strength of lenses. The other gentleman had early acquired the ability to see perfectly well at great distance, but was almost blind for near objects. With convex spectacles he reads quite well.

"It is false that only old people see poorly at near and the young at distance. Both conditions may occur at all ages. With age, however, the power of changing the view from distance to near weakens, and hence those who had healthy eyes at youth see well only at distance. Furthermore, it is more natural and less tiring to hold the eyes parallel rather than convergent on near objects. Therefore, too, tired old eyes remain focused for distance. Those who do much close work in their youth become myopic."

## Comment

Spectacles were invented 300 years before Kepler wrote the paragraphs above, but many objected to their use for various reasons. To pious men, the use of man-made contrivances to improve on God's work seemed preposterous. Others feared damage to the eye by looking through them. Georg Bartisch,[9] the oculist, warned against their use for he could not conceive an eye seeing better with something in front of it than through empty space. His opinion reflects perhaps the imperfect art of lens manufacture.

The scientific foundation which Kepler gave to the function of spectacles did not help popularize their use. Those who were literate and rich enough to read scientific books such as Kepler's wanted no part in the mundane business of making and selling spectacles. Those who peddled spectacles did not read, nor could they understand the appropriate books if they did. The manufacture of optical lenses lacked standardization, marketing was haphazard, and above all, there was no way to arrive at one's need of spectacles except by trial and error.

Ocular astigmatism was described by

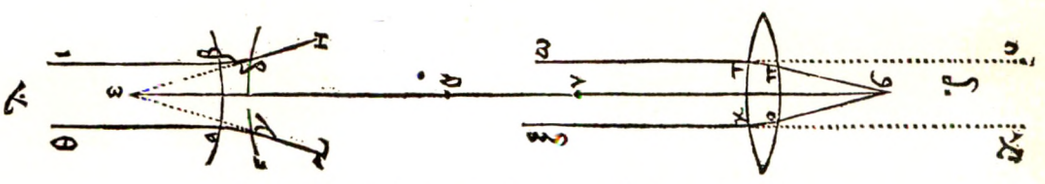


Fig. 8 (Mark). The action of concave and convex spectacles.

Thomas Young 200 years later, and the whole field was most lucidly summarized by Franz Donders[10] in 1864. It is only in the past 100 years that spectacles are applied, at least theoretically, in a truly rational manner.

### Accommodation

"It is impossible for the retina, which is immobile within the eye, to receive clear images simultaneously from near and far. Some see well at distance, some at near. Those who see everything confused have diseased eyes due to faulty structure. In those who see everything distinctly, either the retina or the lens must change its position relative to one another.

"It is probable that in young and healthy eyes the globe is alternately compressed and dilated at the equator when vision shifts to different distances. In this manner, the fundus moves farther or nearer to the lens. It also corresponds to the constriction and dilation of the pupil during this act. The ciliary processes, anchored centrally at the lens, function as a muscle: When they contract, the equator is pulled inward and the globe becomes elongated, removing the fundus backwards to focus the retina for near objects. The opposite occurs when the eye looks at the distance. This is also why the ocular humors (except the lens) are fluid and compressible."

### Comment

It would have required the wildest imagination of a physicist in 1600 to suppose that a lens, including the crystalline lens, could change its form and power; the compressible globe was much closer to observable and possible facts. In addition, the supposed origin of the ciliary processes from near the equator facilitated the notion that their contraction would act upon it. Even so, Kepler's theory of accommodation still holds true for a number of animal species. In man, the actual mechanism was ascertained 250 years later, when tools for observation became available and minds were ready for the observed data.

With the dynamic theory of accommodation, Kepler's work on vision reached its climax—a work which began by studying the effect of lenses upon light, and then applying the observed phenomena to the human eye. The endeavor followed a systematically chartered plan, from one object point to an extention of that point—from the cornea in front to the retina in back, from the optic nerve head centrally to the retinal periphery. And once the static conditions in the normal eye were known, the elucidation of pathologic deviations followed as a matter of course, and even dynamic changes could be conceived.

Kepler reaped a rich harvest by using a deductive method, for, as he told a friend, he was no empiricist concerned with the accumulation of observed data. As such he could hardly have published his work in a modern biological journal that insisted on "original data" and "documented facts." But, as Huxley wrote, "those who refuse to go beyond the facts rarely get as far."

### Summary

A rendition from primary sources of Johannes Kepler's work pertaining to ophthalmology is presented on the anniversary of his 400th birthday. This includes his ideas on ocular anatomy, the dioptrics of the eye, physiologic optics, the nature of the refractive errors, and the mechanism of accommodation.

Kepler's work affords us a good perspective of the state of knowledge about the eye and vision at a time when rational science was emerging from darkness. In addition, it accurately reflects the entire man: his successful struggle to rid himself of old modes of reasoning, the helplessness of his deductive method in face of faulty data, and finally the utter irrelevance of his momentous discoveries to the practice of ophthalmology then and for centuries thereafter.

ACKNOWLEDGMENT

Figure 1 is presented through the courtesy of the Yale Medical Library. Figures 2, 3, 4, and 8 are presented through the courtesy of the Yale-Beinecke Rare Book Library.

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OPHTHALMIC MINIATURE

Nothing you lack to make your outward eye
Totally blind, for what is seen by all
To be a stone you seek to glorify,
A senseless piece of stone that you would call
A god! Put out your hand and let it fall
Upon it, touch it, taste it! You will find
Your hand says "Stone!" although your eyes are blind.

Geoffrey Chaucer
The Second Nun's Tale
*Canterbury Tales*

# ELECTRON MICROSCOPY OF POSTERIOR POLYMORPHOUS DEGENERATION

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Posterior polymorphous degeneration is clinically characterized by peculiar opacification of the posterior limiting layers of the cornea. Both sporadic[1] and familial[2] cases have been reported, and most authors state that the disease is nonprogressive.[2]

This report concerns the case of a patient with a strong family history of posterior polymorphous degeneration, who showed a progressive course and anomalies of the angle. The surprising feature was the presence of cells on the posterior surface of the cornea having the characteristics of epithelium.

## CASE REPORT

*Case* 1—A 35-year-old white man was first seen at the age of 15 years by Dr. D. G. Cogan, who made a diagnosis of "peculiar dystrophy of the posterior corneal surface." Over the course of years, the corneal opacities gradually increased (Fig. 1). At the age of 33 years, the patient developed painful bullous keratopathy in the left eye. Gonioscopy revealed that extensive areas of the trabeculum were covered by broad synechiae. However, the intraocular pressure was normal. The rest of the examination was normal except for the presence of a Marcus Gunn jaw-winking phenomenon on the left side. There had never been injury or surgery to the eyes.

The family pedigree is noted in Figure 2. Of particular interest is the patient's brother, who also showed broad peripheral synechiae and progressive disease resulting in decompensation of the posterior limiting layers of the cornea and epithelial edema. Because of painful bullous keratopathy, a penetrating keratoplasty was carried out in the left eye. The excised corneal button was studied histologically and electron microscopically.

*Histopathologic findings*—One-half of the button was fixed in 10% formalin and embedded in paraffin for histological study. Paraffin sections stained with hematoxylin-eosin and with periodic acid Schiff reaction revealed that the cornea had a loosely attached epithelium, edematous stroma and a thickened Descemet's membrane. The thick Descemet's membrane consisted of a thin layer of strongly PAS-positive membranes anteriorly and a thick layer of lamellated substance posteriorly. The endothelium was uneven in thickness (Fig. 3). No wart was found in the Descemet's membrane. No scar tissue or inflammatory cells were found in the corneal button. Cresyl violet staining showed normal metachromasia in the stroma. No abnormal substance was deposited in the stroma.

*Electron microscopic findings*—The other piece of the button was fixed in 4% glutaraldehyde solution in phosphate buffer (pH 7.2) for 20 minutes at room temperature. The tissue was cut into smaller pieces and postfixed in 10% osmium tetroxide for 90 minutes at a cold temperature. The tissue was dehydrated in ethyl alcohol, treated with propylene oxide and embedded in an epoxy resin. Thin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope.

A surprising abnormality was found by electron microscopy. Cells covering the posterior surface of the cornea were found to have all the characteristics of epithelium instead of endothelium.

The cells were extremely flat and formed a layer two to three cells thick (Figs. 4 and 5). At several areas, cells formed clumps of four to five cell thickness. The cells had elongated nuclei and thin cytoplasm. At the basal zone, the cells were flat and had occasional basal infoldings and hemidesmosomes. The apical surfaces of the cells which faced the anterior chamber had massive microvilli (Figs. 6 and

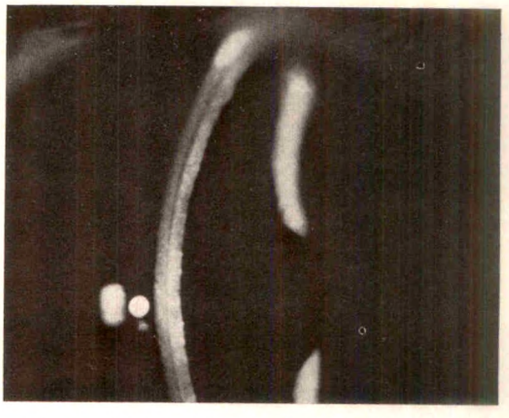


Fig. 1 (Boruchoff and Kuwabara). Slit lamp view of the cornea. This photograph was taken one year before the surgery.

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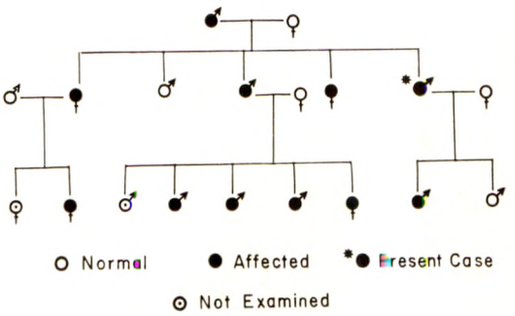



Fig. 2 (Boruchoff and Kuwabara). Pedigree of the family of the case.

7). The microvilli were taller than the plicae of the normal superficial epithelium of the cornea and were irregular in size. Lateral cell membranes were joined by numerous desmosomes which had prominent tonofibril attachments (Fig. 7). No tight junctions were found at the apical ends. The cytoplasm had a relatively electron dense matrix in which keratofibrils were seen abundantly. The fibrils formed bundles of varying sizes. Microorganelles were extremely sparse. Mitochondria, endoplasmic reticulum and Golgi apparatus were rare or entirely missing from the cytoplasm. Only a small number of glycogen particles was seen among the keratofibrils. Occasional cells, especially in the area of the clumpings, were larger and contained inclusion bodies, which presumably were phagocytized debris (Fig. 8).

A thick Descemet's membrane measuring about 30μ had formed between the lining cell of the anterior chamber and the stroma (Fig. 5). This consisted of a thin (3μ) portion which was highly PAS-positive light microscopically at the anterior limit and a thick (15-25μ) layer of abnormal collagen fibers with a minimal mucoprotein content in the posterior region. The thin portion of the Descemet's membrane was uniform in thickness and consisted of coarse granular substances which formed 100 nm spacings in several locations (Fig. 9). The fine structural appearance of the membrane was identical to that of the anterior portion of the Descemet's membrane of an adult cornea. The abnormal collagen layer consisted of irregular layers of fine fibrils, short collagen fibers and basal lamina substance (Figs. 5 and 9). A thick basement membrane was formed beneath the cells. The fibrillar substance formed two kinds of banded structures. One was made of aggregated short fibrils with a banding of 100 nm spaces, and the other was formed of longer (1-3μ) fibrils with 70 mm spacings. These components were scattered throughout the tissue without any specific pattern of distribution (Fig. 9). No cell, fibroblastic or otherwise, was found in this layer.

The swollen stroma showed a less distinct lamellar arrangement of collagen fibers. Spaces between collagen fibers were widened. Fine fibrillar substance was abundantly found between the collagen fibers and between the lamellae. The stroma cells were rounded and contained sparse microorganelles. Basal laminar substance was found abundantly accumulating around the stroma cells (Fig. 10).

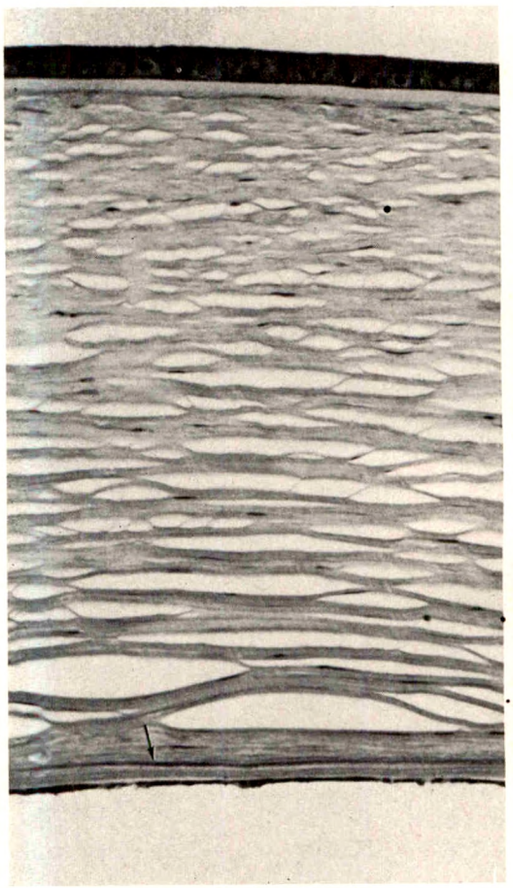


Fig. 3 (Boruchoff and Kuwabara). The central portion of the corneal button. The stroma is edematous. A thin PAS-positive layer (arrow) and thick PAS-negative layer form the Descemet's membrane (paraffin section, PAS and hematoxylin stain, ×80).

Fig. 5 (Boruchoff and Kuwabara). Low magnification electron micrograph of the posterior portion of the cornea. The surface cells are of an epithelial type. An abnormal membrane is formed between the cell layer and the original Descemet's membrane. This anterior portion of the Descemet's membrane is uniform in thickness and appearance (×4400).

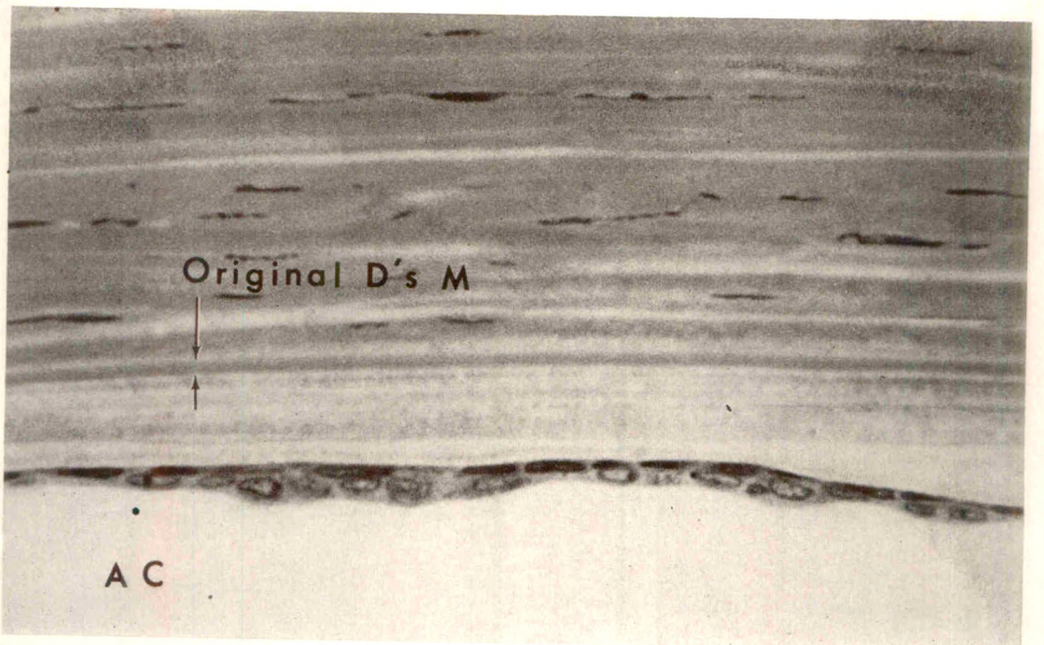
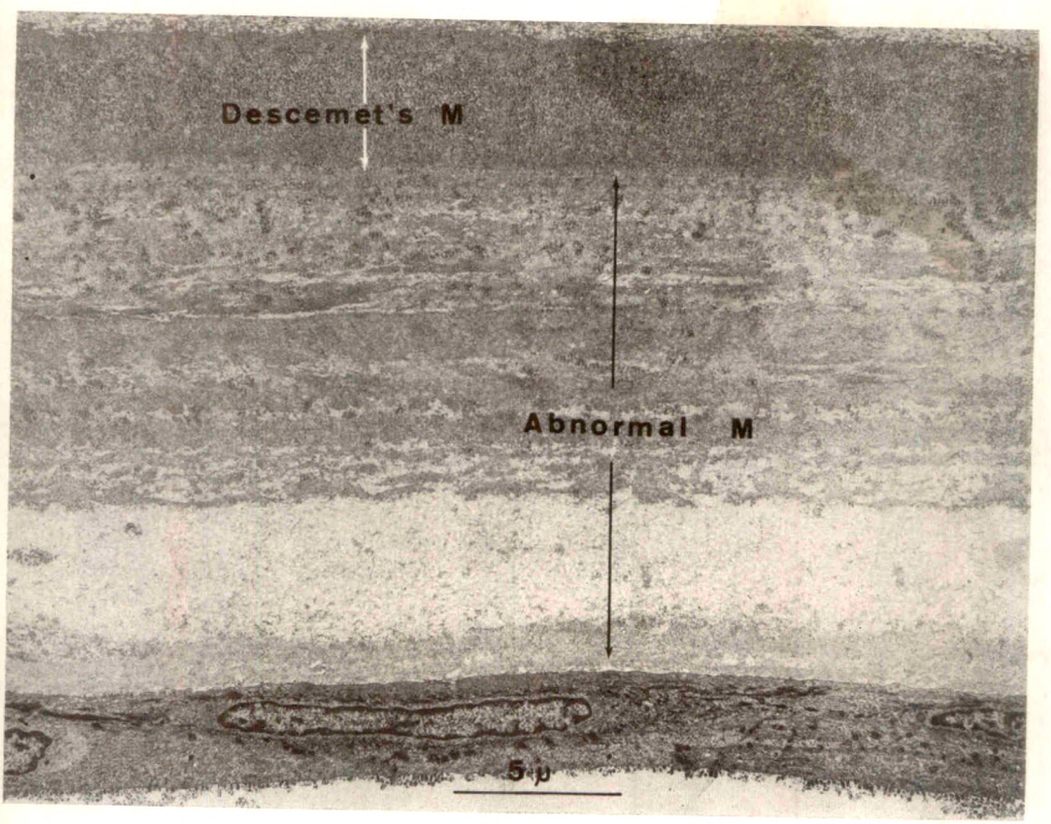



Fig. 4 (Boruchoff and Kuwabara). The cells covering the posterior surface of the cornea form a layer two to three cells thick. A thick acellular layer is formed between the thin Descemet's membrane and the posterior surface cells. Epoxy section, 0.5μ thick (toluidine blue, ×400).



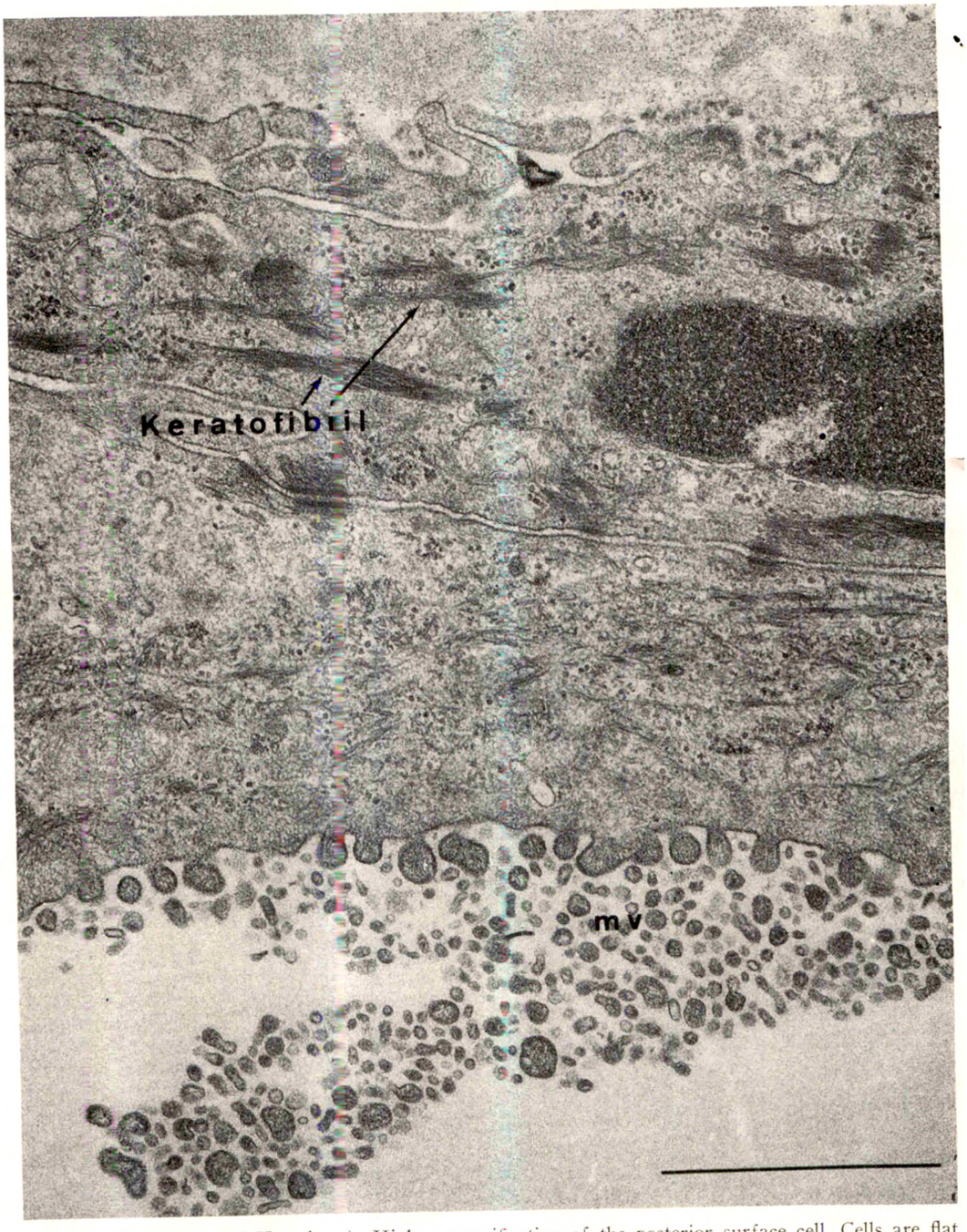



Fig. 6 (Boruchoff and Kuwabara). Higher magnification of the posterior surface cell. Cells are flat and joined by numerous desmosomes. Microvilli are seen abundantly at the apical end. The base of the cell is infolded. Hemidesmosomes are infrequent. The cytoplasm contains keratofibrils (×40,000).

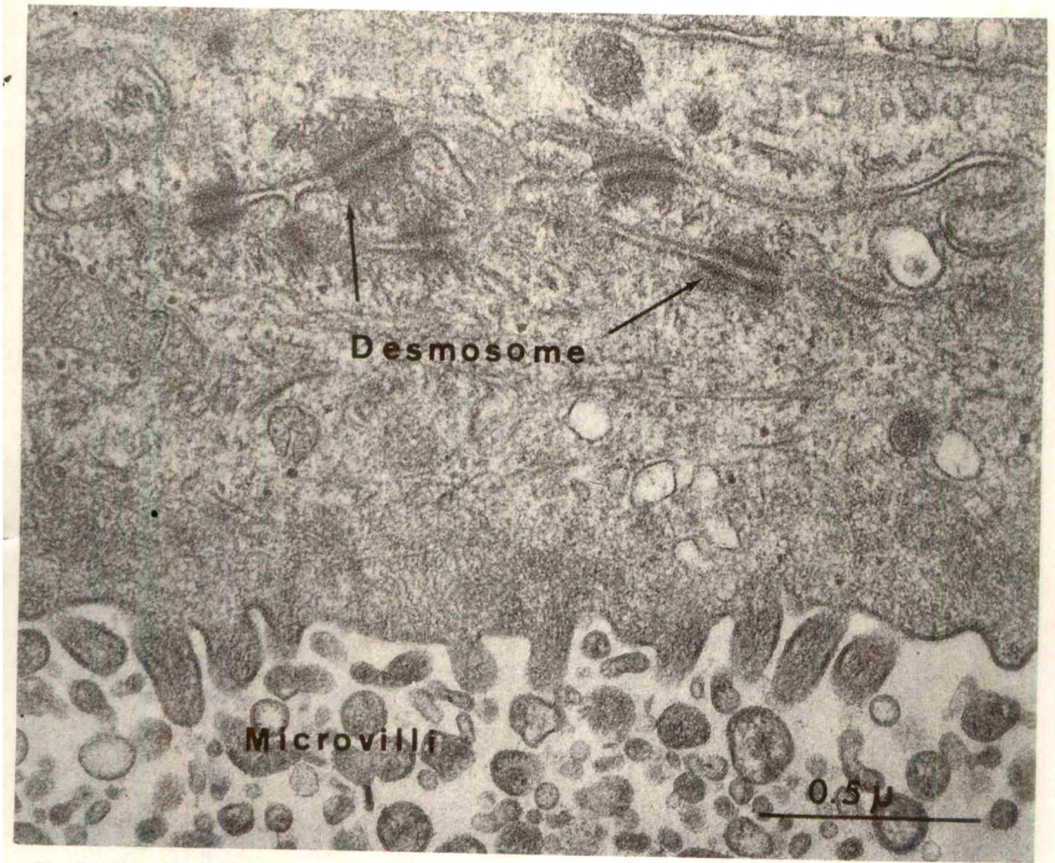



Fig. 7 (Boruchoff and Kuwabara). Higher magnification of the apical portion of the posterior surface cell. Microvilli are in varying sizes. Desmosomes between the adjacent cells are conspicuous. The cytoplasm contains tonofibrils, vacuoles and a little glycogen. Metabolically active microorganelles are sparse (×60,000).

The epithelium at the anterior corneal surface was loosely attached to the underlying connective tissue. The basal cells had markedly infolded cytoplasm at the base and the basement membrane was incomplete. The cytoplasm of the basal cells was electron lucent and contained sparse microorganelles. The wing and superficial cells appeared to be normal.

## Discussion

Since the patient had no history of ocular injury or surgery, the presence of epithelial cells on the posterior surface of the cornea was unexpected. The cytoplasmic appearance of these cells definitely indicated that they were cells of the epithelium: microvilli, abundant keratofibrils, desmosomes and sparse microorganelles. Characteristic structures of the endothelium, such as rich microorganelles, apical tight junctions and flat apical surfaces, were totally absent.

The origin of the epithelium on the posterior surface of the cornea has not been demonstrated in the present study and is subject to speculation. The most likely possibility is an embryonal displacement of the epithelial cells into the anterior chamber. Intraocular displacement of the ectodermal cell can occur when the optic cup is formed at the earliest stage of the development of the eye. Since the case presented here has a strong familial dominancy and has other abnormalities in the anterior chamber, an unspecified developmental disorder may have taken place in the earliest stage of formation of the eye.

Members of the family also showed vari-

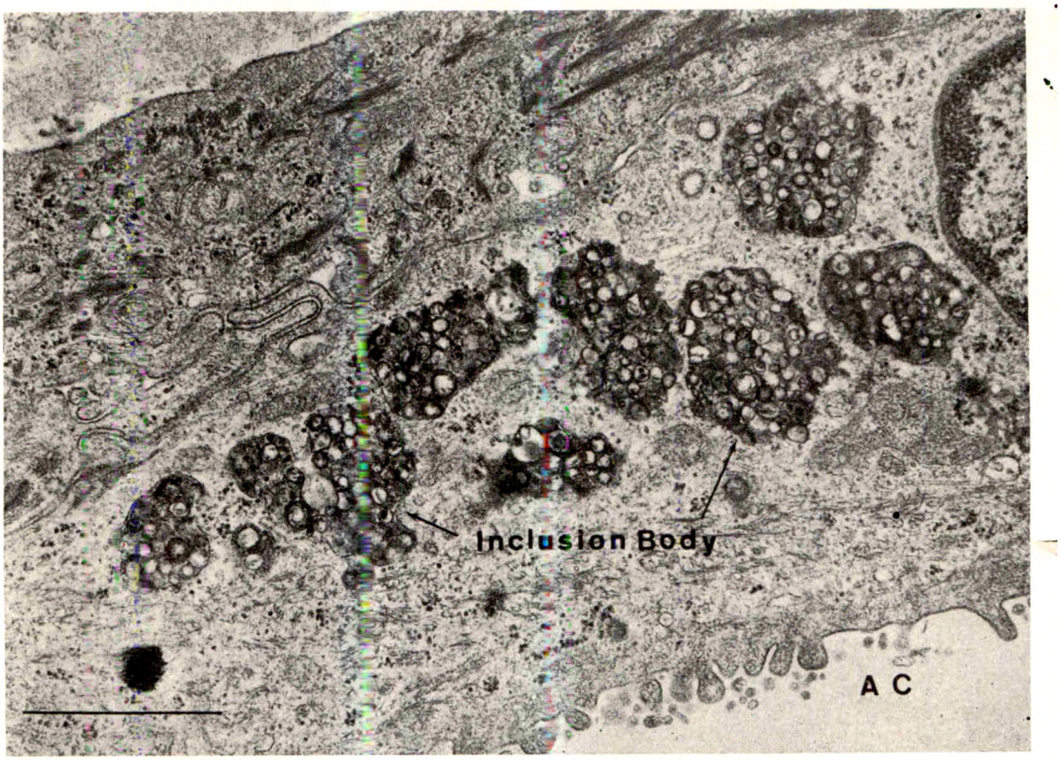



Fig. 8 (Boruchoff and Kuwabara). Some epithelial cells contain inclusion bodies, which appear to be degenerating cell debris (×27,000).

ous degrees of congenital abnormalities, ranging from rare scattered vesicles to widespread opacification of the posterior cornea. The presence of broad synechiae in the patient and other members of his family suggests some variation of the "faulty cleavage syndrome."[3] The presence of synechiae associated with posterior polymorphous dystrophy has been mentioned in the literature,[1] and seen by us in other patients with this disease not related to the family herein reported. There may be a spectrum of diseases with the common denominator related to the formation of the posterior surface of the cornea. The displacement of the ectodermal cell may be one of these embryonal abnormalities. There are other conditions—e.g., Rieger's anomaly (primary mesodermal dysgenesis of the iris), which has a high incidence of central corneal involvement (62 of 170 eyes)[4]; Peter's anomaly (mesodermal dysgenesis of the cornea), which shows a high incidence of synechiae between cornea and iris, and often correctopia and iris hypoplasia; and Chandler's syndrome (cornea guttata, iris atrophy and glaucoma)—perhaps all of these are varying manifestations of a developmental fault. It would prove most interesting to study the posterior limiting layers of these conditions.

Another possibility is a transformation of the endothelial cells into the epithelium. Yet endothelium and epithelium have no close developmental relationship, and pathologic endothelial cells in various clinicopathological and experimental conditions examined by us have never shown any suggestion of such a transformation.

The epithelial cells at the posterior corneal surface of the present case appear similar to

that of the downgrowth of epithelium in the anterior chamber following cataract surgery. With the clinical course and the history of the patient, this possibility can be ruled out. The downgrowth of corneal epithelium has a relatively rapid growth rate and the cells contain more metabolically active microorganelles. The cytologic findings of the epithelium in the posterior cornea of the present case suggest that these cells are metabolically inactive. The cytoplasm contains almost no active microorganelles. This may explain the slow clinical course in this patient.

The presence of the thin Descemet's membrane suggests that the cornea was formed by normal endothelial cells in the early developmental stage. Judging from the thickness and uniformity of the Descemet's membrane, the function of the endothelium ceased and was replaced by epithelium in an early infantile period. Since the structure of the whole thickness of the thin Descemet's membrane is identical to that of the anterior half of an adult membrane, the membrane appears to have aged without adding new normal substance. After the replacement of

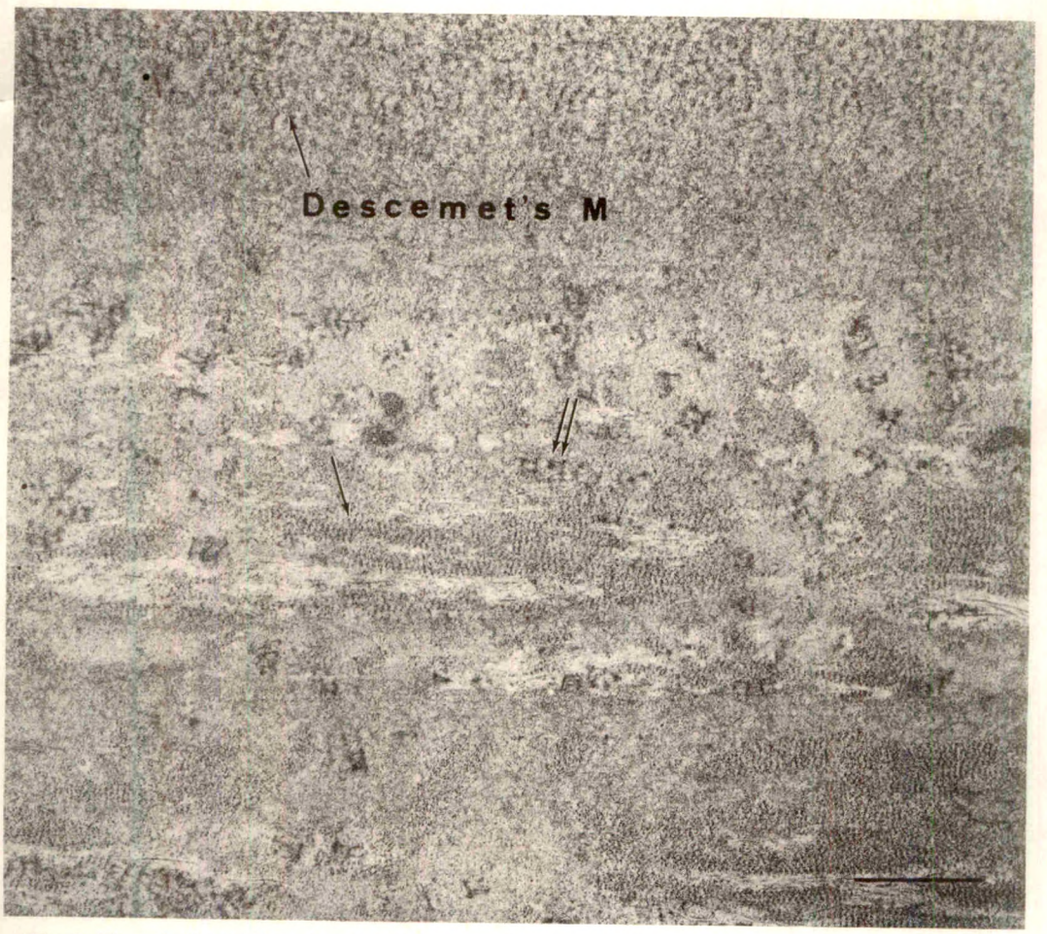



Fig. 9 (Boruchoff and Kuwabara). Higher magnification of the abnormal collagen membrane and the Descemet's membrane. The Descemet's membrane consists of coarse granular substances which are forming 100 nm spacings. The abnormal membrane is made of a mixture of fibrils, collagen fibers and basal lamina substance. Fibril materials are forming 100 nm spacings (double arrow) and 30 nm bandings (single arrow). Whitish portions are mainly collagen fibers (×17,000).

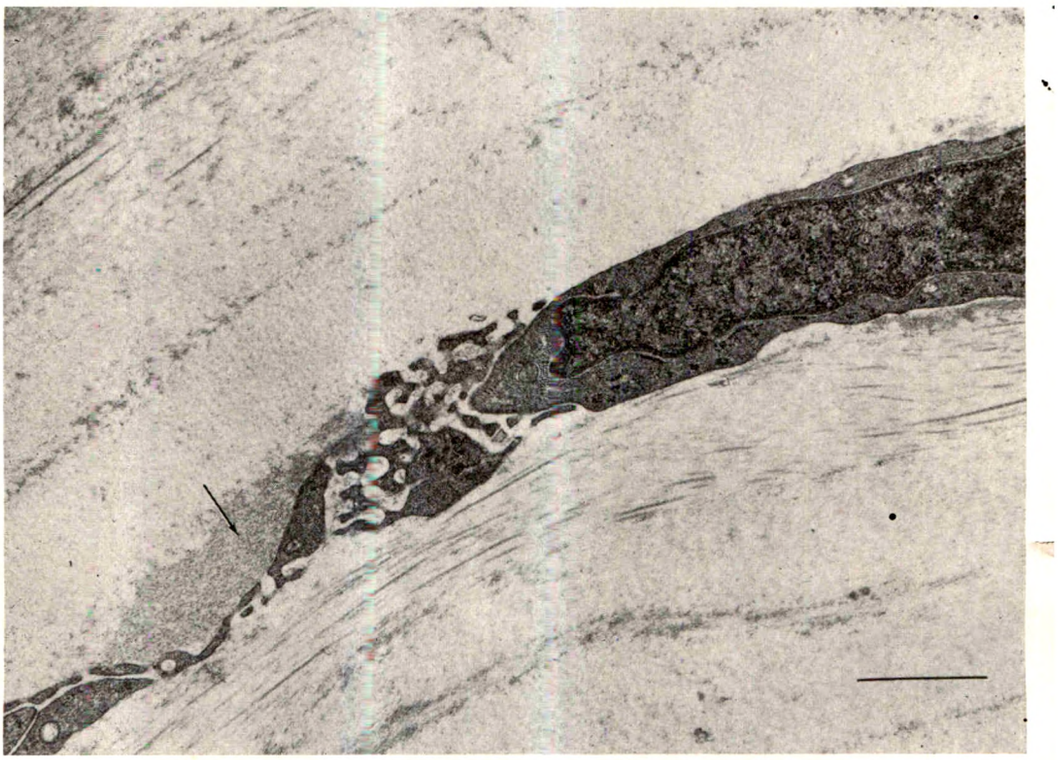


Fig. 10 (Boruchoff and Kuwabara). Stroma of the edematous cornea. Lamellar arrangements of collagen fibers are irregular. Stroma cell is rounded. Basal laminar substance (arrow) is seen abundantly around the cell (×17,000).

the endothelium by the epithelium, a thick pathologic portion appears to have formed posterior to the original Descemet's membrane. The appearance of this layer is similar to that of a nonspecific subepithelial or posterior accessory membrane. Abnormal collagen fibers and fibrillar substances form aggregations and bandings in various shapes. However, these structures may not have any specific correlation to the cause of this disease. A similar pathologic membrane in the posterior cornea was demonstrated recently in a case of hereditary corneal edema.[5]

It must be emphasized that the pathologic findings of the posterior zone of the cornea of the present case differ from those of the common endothelial dystrophy. Pathologic endothelium produces a thickened or multilayered Descemet's membrane instead of being buried as a thin layer.

It should be pointed out that the abnormal membrane contains no cells other than the epithelium at the posterior surface. This suggests that the abnormal collagen fibers have been produced by the aberrant epithelium. Analogous production of collagen fibers by the epithelium has been shown in developing avian corneas.[6] Pathologic findings in the present case support the theory of an epithelial origin for collagen formation.

## Summary

A corneal button from a case of hereditary posterior polymorphous degeneration was studied electron microscopically. The abnormal cells at the posterior surface of the cornea were found to have the characteristics of epithelial cells.

The pathogenetic origin of the cell may be

due to displacement of the ectodermal cells occurring at the earliest stage of the optic cup formation. This disease may be a part of a large spectrum of malformations of the anterior portion of the eye in the early developmental stage.

Electron microscopic study suggests that the accessory collagen membrane has been produced by the aberrant epithelial cells.

ACKNOWLEDGMENT

The authors thank Dr. David G. Cogan for his constant interest and criticism on this investigation.

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OPHTHALMIC MINIATURE

Dirty lenses affect vision and they can upset a driver's judgement. An illustration of this was given by Paul Frere, the Belgian racing driver. He found he was lapping a circuit two seconds slower than normal, which does not sound much until you realize that races of 50 or 60 laps are often won or lost by a single second. Paul Frere could find no reason for his reduced speed until he examined the goggles he was wearing. They were scratched. He changed to an unscratched pair and his times went back to normal. The scratching had upset his judgement and therefore reduced his speed.

Pat Moss and Eric Carlsson
*The Art and Technique of Driving*
Heinemann, 1965

# HISTOPATHOLOGIC FINDINGS IN CORNEAS FOLLOWING LENS EXTRACTION AND RESULTS OF KERATOPLASTY FOR APHAKIC BULLOUS KERATOPATHY

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Although in the vast majority of lens extractions the results of surgery are gratifying both to patient and surgeon, in a small number of cases, postoperative corneal problems leave the patient with severely impaired vision. Even in corneas that were clear, Miller and Dohlman[1] reported a demonstrable increase in corneal thickness following lens extraction in 76% of 50 unilaterally aphakic patients whom they studied. In this paper the histopathologic findings in a series of corneal specimens obtained from aphakic eyes are presented, together with the results of corneal transplant surgery.

## MATERIALS AND METHODS

Twenty-eight consecutive corneal buttons received in the ophthalmic pathology laboratory at New York University from eyes which had had previous lens extraction were studied. The specimens were submitted by several different contributors, and often the cataract surgery had been performed by a surgeon other than the one from whom the subsequent corneal specimen was obtained. Thus, histories relating to the original cataract surgery were not considered sufficiently reliable to permit a reasonable estimation of complications at the time of surgery.

The corneal buttons were fixed in Formalin. All were bisected (except for a 2-mm diameter specimen which was removed at the time of prosthokeratoplasty) and embedded in paraffin. Microscopic cross-sections were stained with hematoxylin and eosin, periodic acid Schiff, and special stains when indicated. The results of corneal transplant surgery were ascertained in all cases.

## RESULTS

Table 1 lists the principal histopathologic finding in each of the 22 full-thickness and six lamellar specimens. Bullous keratopathy secondary to endothelial degeneration was by far the most common abnormality. It was the only category large enough to provide significant follow-up data. There were seven other categories with only a small number in each.

*Bullous keratopathy secondary to endothelial degeneration*—Seventeen of the corneal specimens were obtained at the time of full-thickness keratoplasty for bullous keratopathy (Fig. 1). In each of these, in addition to bullous separation of epithelium from Bowman's membrane, the most striking finding was severe degeneration or virtual absence of corneal endothelium (Fig. 2). In all but two cases this was true in the presence of a normal Descemet's membrane without posterior excrescences. In one of

TABLE 1

PRINCIPAL HISTOPATHOLOGIC FINDINGS

| Pathology | Penetrating | Lamellar |
|---|---|---|
| Bullous keratopathy, secondary to endothelial degeneration | 17 | 2 |
| Pannus | 1 | 1 |
| Hypertrophic scar | | 1 |
| Stromal overgrowth | 2 | |
| Epithelial downgrowth | 1 | |
| Intracorneal hematoma and descemetocele | 1 | |
| Mooren's ulcer | | 1 |
| Band keratopathy | | 1 |
| Total | 22 | 6 |

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those two cases (Fig. 3), part of Descemet's membrane had been torn away. This is presumed to have happened at the time of lens extraction. The possibility of its occurrence during the keratoplasty was ruled out by an accumulation of pigment on the back of the exposed part of the stroma. The other had a laminated Descemet's membrane.

In some instances the epithelium was missing in the histologic sections and there was a diffuse infiltrate of acute inflammatory cells in the stroma—an acute keratitis secondary to ruptured epithelial blebs.

Two of the specimens in which the primary histologic finding was bullous keratopathy were lamellar specimens. Although the endothelium was, of course, not seen, similar degeneration might reasonably be expected.

The results of the transplant surgery in these 19 cases are summarized in Table 2. Despite the severely degenerated host endothelium, which might lead one to expect poor visual results, eight of the 17 penetrating grafts remained clear during a follow-up period ranging from six months to four years. Median age and duration of follow-up (Table 3) were similar for patients with clear grafts and with failures. Of the eight which were clear, the fellow eye in six cases was noted to have a normal cornea while two had cornea guttata. Of those which failed, the fellow eye had a normal cornea in three instances and an abnormal cornea in six. The abnormality in four instances was cornea guttata; one had an opaque cornea; another

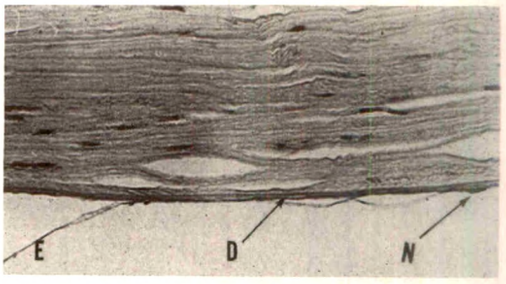



Fig. 2 (Kurz). Severe degeneration of corneal endothelium in a 65-year-old woman with bullous keratopathy nine months following lens extraction. Strand of degenerated endothelium (E) is separated artifactitiously from Descemet's membrane (D). One endothelial nucleus (N) remains in this field (hematoxylin and eosin, ×192).

was an aphakic eye which had had a keratoplasty.

Of the nine grafts which failed six were described simply as "opaque," two had epithelial edema, and one, which developed a pneumococcal ulcer three weeks postoperatively, became opaque and vascularized. None had better than 20/400 vision.

As one might expect, neither of the two lamellar grafts for aphakic bullous keratopathy remained clear. The first was performed in preparation for a prosthokeratoplasty. The second was done for relief of pain and structural improvement of a cornea on which a previous Salleras cauterization of Bowman's membrane had been done. The latter graft, initially clear, had developed epithelial edema seven months postoperatively. The cautery punctures in the excised speci-

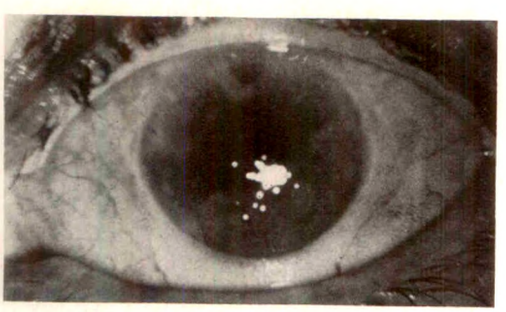


Fig. 1 (Kurz). Bullous keratopathy in a 76-year-old white woman one year following lens extraction.

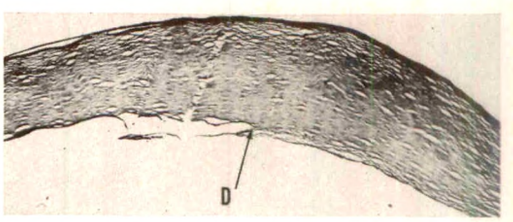



Fig. 3 (Kurz). Part of Descemet's membrane absent from cornea of a 65-year-old white man with bullous keratopathy and secondary glaucoma eight months following lens extraction. Descemet's membrane (D) is present only to left of arrow (PAS, ×30).

TABLE 2

BULLOUS KERATOPATHY

| | | Cornea of Fellow Eye | |
|---|---|---|---|
| | | Normal | Abnormal |
| Penetrating: | | | |
| Clear | 8 | 6 | 2 |
| Failure | 9 | 3 | 6 |
| Lamellar: | | | |
| Clear | 0 | 0 | |
| Failure | 2 | 2 | |
| Total | 19 | | |

men (Fig. 4) extended considerably deeper than Bowman's membrane.

## COMMENT

Dohlman and Boruchoff[2] state that in most cases of persistent corneal edema after cataract extraction some element of endothelial dystrophy was present as evidenced by guttate changes on the posterior corneal surfaces of both corneas. In the present series, less than half of the cases were said to exhibit cornea guttata in the fellow eye and none of the pathologic specimens had the posterior excrescences of Descemet's membrane characteristic of endothelial dystrophy.

The satisfactory results of penetrating keratoplasty in nearly half of these cases of aphakic bullous keratopathy despite the very poor condition of the host endothelium is similar to results recently reported by Foster and Fine.[3] In the eyes with aphakia and corneal edema, 46 out of 94 penetrating keratoplasties were transparent.

Stocker and Irish[4] reported the long-term results of 12 initially successful corneal grafts for Fuchs' endothelial dystrophy. One case after another eventually developed edema; all were cloudy nine years postoperatively. Their conclusion was that "the endothelium of the graft had probably exhausted its lifetime and diseased endothelium of the recipient was not able to replace the dying endothelium of the graft by normal cells." A similar eventual outcome might well be expected in the cases reported here because of the similarity of the basic problem of diseased host endothelium.

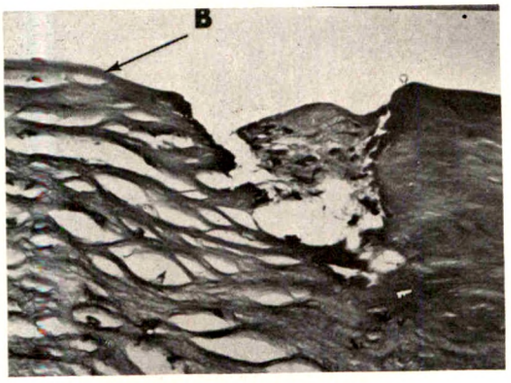



Fig. 4 (Kurz). One of numerous cautery puncture sites in cornea of 67-year-old man three years following lens extraction. Cauterization of Bowman's membrane was performed for bullous keratopathy two months prior to the lamellar keratoplasty from which this specimen was obtained. Epithelium is absent. Puncture extends well beyond Bowman's membrane (B) and into stroma. There is early fibrous connective tissue healing of this cautery site (hematoxylin and eosin, ×192).

It would have been most interesting to correlate the age of the donors with the successes and failures of grafts in this group. Unfortunately, under the circumstances of this study, this information is rarely available. Considering the poor condition of the host endothelium, I suspect that the condition of the donor endothelium may play a more important role in grafts of this type than in grafts not replacing corneas with degenerated endothelium.

Foster and Fine[3] found no significant differences in results between penetrating grafts done with donors of four different age groups. Their study included 398 grafts

TABLE 3

RESULTS OF PENETRATING GRAFTS IN BULLOUS KERATOPATHY

| Status | | Median Age | Mean Duration of Follow-up |
|---|---|---|---|
| Clear grafts | 8 | 67 | 18 months |
| Failures | 9 | 71 | 21 months |

in three prognostic categories followed for at least six months. But among their aphakic bullous keratopathy cases, 54.2% were clear in the 72 cases with donors under age 70 years, while 31.8% were clear in the 22 cases with donors over 70 years of age.

It would seem important for persons doing corneal surgery, especially of this type, to keep records of the age of donors.

*Pannus*—Degenerative pannus was the principal finding in one full-thickness and one lamellar specimen. In three additional cases a slight pannus was noted, and was regarded as an incidental finding.

In one case, because of a corneal lesion suspected clinically of being Bowen's disease, a lamellar keratoplasty was performed on a 65-year-old white man 12 years following lens extraction (Fig. 5). Histologic sections (Fig. 6), however, show a thick fibrous connective tissue pannus between Bowman's membrane and a degenerated epithelium. Nodules of epithelium were trapped within the pannus.

Pannus may be related to bullous keratopathy in some instances. Edema fluid elevating the epithelium probably precedes the growth of connective tissue between epithelium and Bowman's membrane.

Both grafts in which pannus was the principal finding failed. Two in which pannus

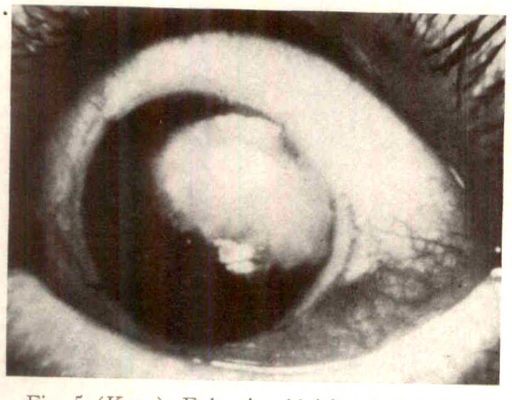


Fig. 5 (Kurz). Enlarging bluish raised lesion on cornea of aphakic patient. Vessels entered the lesion from the upper temporal periphery. Finger-like projections were present on its lower aspect. Clinical diagnosis was Bowen's disease.

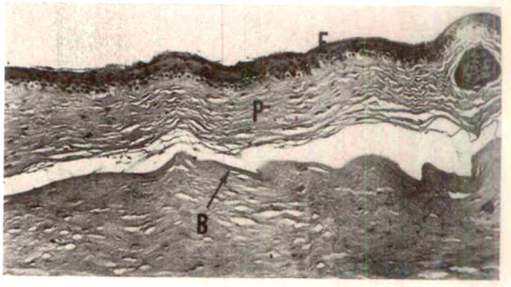



Fig. 6 (Kurz). Thick fibrous connective tissue pannus (P) between epithelium (E) and Bowman's membrane (B). Nodule of epithelium is trapped within the pannus (hematoxylin and eosin, ×75).

was regarded as an incidental finding were included among the unsuccessful penetrating grafts for aphakic bullous keratopathy secondary to endothelial degeneration. The third specimen with an incidental pannus was a lamellar specimen from an eye with band keratopathy. The graft was described as moderately clear four months postoperatively.

*Hypertrophic scar*—A 65-year-old black man developed a large opaque corneal mass with some vascularization involving the temporal two-thirds of the cornea (Fig. 7). At the time of cataract surgery three years prior



Fig. 7 (Kurz). Lamellar keratoplasty specimen, 9.5 mm in diameter, removed from a 65-year-old black man three years following lens extraction. A 6.7-mm diameter round, elevated, vascularized lesion was eccentrically located on the anterior surface.

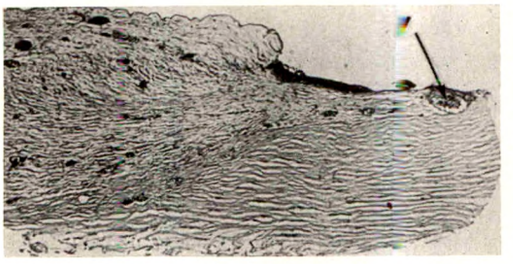


Fig. 8 (Kurz). Vascularized lesion occupies nearly full thickness of lamellar specimen. Large vessel (V) enters vascularized scar anterior to Bowman's membrane (hematoxylin and eosin, ×39).

to keratoplasty there had been vitreous loss. Postoperative vitreous touch followed by corneal edema preceded the growth of the mass.

Histologic findings (Fig. 8) showed an elevated vascularized scar occupying virtually the full thickness of the lamellar specimen. Vessels entered the periphery anterior to Bowman's membrane, suggesting that the lesion began as a pannus, and then branched out to fill the entire vascularized scarred area.

*Stromal overgrowth*—A 49-year-old white man was seen with advanced total bullous keratopathy almost two years following lens extraction. The clinical appearance (Fig. 9) resembled the cases of bullous keratopathy secondary to endothelial degeneration. Microscopic sections, however, showed a thin fibrous connective tissue membrane posterior to Descemet's membrane (Fig. 10) in addition to bullous keratopathy. This layer of stromal overgrowth stained with blue with Masson trichrome.

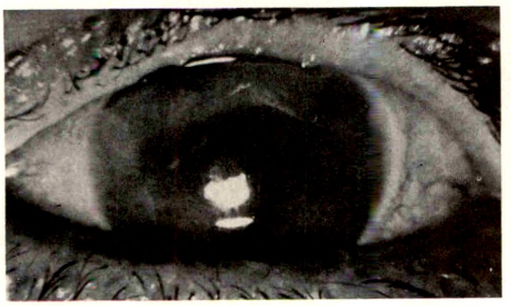


Fig. 9 (Kurz). Hazy cornea from advanced bullous keratopathy in a 49-year-old white man nearly two years following cataract surgery.

The second specimen exhibiting stromal overgrowth as its principal finding was a 2-mm diameter corneal button removed at the time of prosthokeratoplasty. The patient was an 80-year-old white man with a history of wound rupture, delayed reformation of the anterior chamber, glaucoma, keratitis and corneal opacification. In this one specimen (Fig. 11) there were scarring and vascularization, stromal overgrowth, and epithelial downgrowth.

In one other case, stromal overgrowth was an incidental finding associated with an epithelial cyst.

The subject of corneal stromal overgrowth, well known following penetrating keratoplasty, but infrequently recognized as a complication of lens extraction, was reviewed by Friedman and Henkind.[5] They mentioned the hypothesis that formed vitreous in contact with the wound might provoke a chronic inflammatory reaction and thus fibroplasia. Perhaps of greater importance is the fact that formed vitreous prevents endothelialization of the posterior aspect of the wound, leaving stromal fibroblasts free to proliferate in the tissue culture-like aqueous (Kurz and D'Amico[6]).

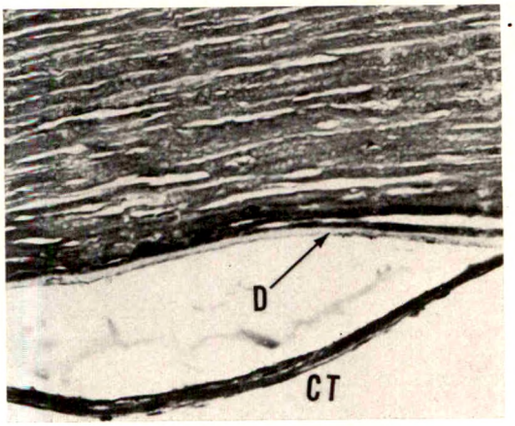
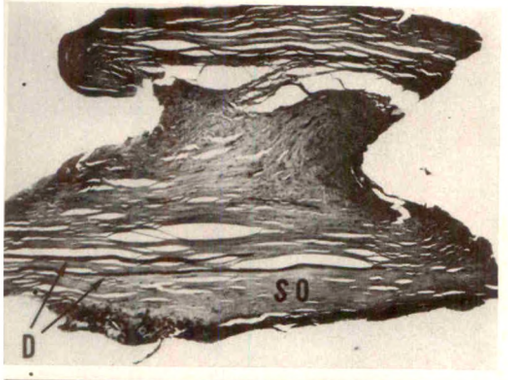



Fig. 10 (Kurz). Thin layer of fibrous connective tissue (CT) lines posterior aspect of Descemet's membrane (D). Areas of separation are probably artifactitious (Masson, ×192).

*Epithelial downgrowth*—A 74-year-old white man whose vision became diminished from bullous keratopathy one year after lens extraction with peripheral iridectomy was noted to have a large iris cyst superiorly. A penetrating keratoplasty was performed three years following the cataract surgery. Microscopic examination (Fig. 12) showed surface epithelium lining a portion of the posterior corneal surface. Descemet's membrane was thickened and laminated, endothelium was largely absent, and an incidental stromal overgrowth was present. A thicker layer of surface epithelium covered much of the atrophic iris which was excised at the same time.

This was the only specimen in the series exhibiting epithelial downgrowth as the principal histologic finding. In one other case, epithelial downgrowth was present. Although any epithelial downgrowth assumes major significance clinically, in the histologic sections of this case it was overshadowed by stromal overgrowth.



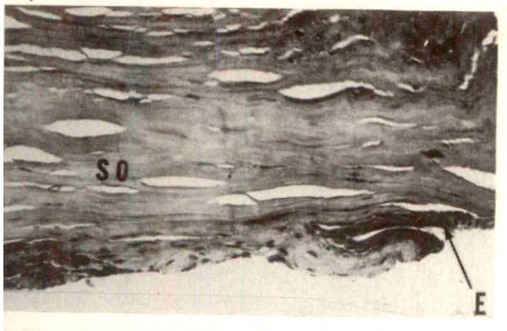
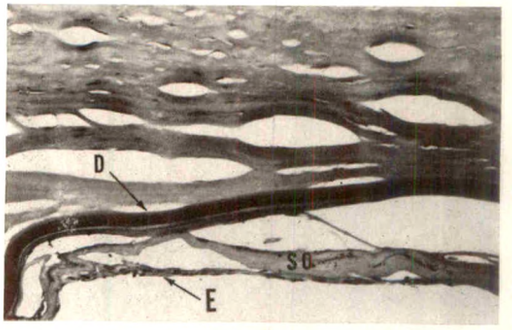




Fig. 11 (Kurz). Top: Corneal button removed at time of prosthokeratoplasty. Appearance of two Descemet's membranes (D) may be due to folding. Fibrous connective tissue extends around end of Descemet's membrane to form plaque of stromal overgrowth (SO) (Pas, ×39). Bottom: Surface epithelium (E) is adherent to posterior aspect of stromal overgrowth (PAS, ×192).



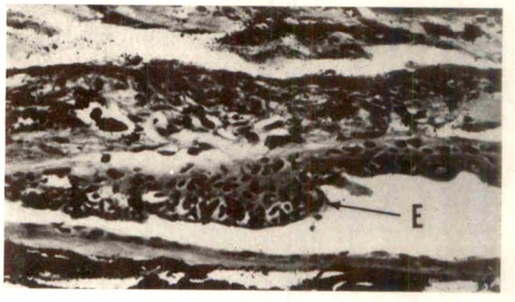




Fig. 12 (Kurz). Top: Epithelial downgrowth (E) and stromal overgrowth (SO) on posterior aspect of Descemet's membrane (D) one year after cataract surgery (PAS, ×192). Bottom: Thicker layer of epithelium lines portion of folded iris (PAS, ×192).

*Intracorneal hematoma and descemetocele*—An extraordinary case was that of a 72-year-old white man who was said to have undergone an uneventful cataract extraction with an uncomplicated course in the immediate postoperative period. Shortly thereafter, however, he complained of progressive loss of vision with occasional irritation of the eye. Three and one-half months after surgery a blood-stained cornea and central descemetocele were evident clinically (Fig. 13).

Hemoglobin globules scattered in the stroma and positive staining for iron in keratocytes bore out the clinical diagnosis of blood-stained cornea. In addition, surrounding the central descemetocele there was a striking intracorneal hematoma between the

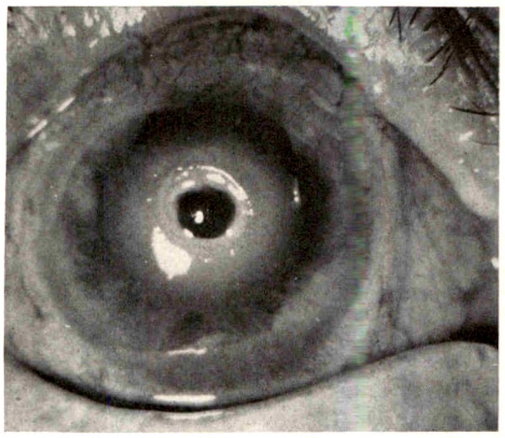


Fig. 13 (Kurz). Central descemetocele and blood staining of cornea three and one-half months after lens extraction.

deepest layers of stroma and Descemet's membrane (Fig. 14).

## Comment

The pathogenesis of the hematoma is unclear. In the eye pathology laboratory at New York University, however, there is one other case (an evisceration specimen and therefore not included in this series) with a hematoma between Descemet's membrane and corneal stroma in an aphakic eye which had also had an iridencleisis and two electrodialyses of an iris cyst. Another (an enucleated aphakic eye) has blood vessels between Descemet's membrane and the deep stroma. Vascularization such as this may have been the source of the hematoma illustrated in Figure 14. Bardy[7] states that deep corneal hematomas, which are much rarer than superficial ones, are usually due to rupture of a deep vessel as in old interstitial keratitis. According to Duke-Elder,[8] these new vessels immediately in front of Descemet's membrane arise from the iris in interstitial keratitis associated with uveitis. No evidence of old interstitial keratitis was seen in the cornea of the fellow eye of the case reported in this series.

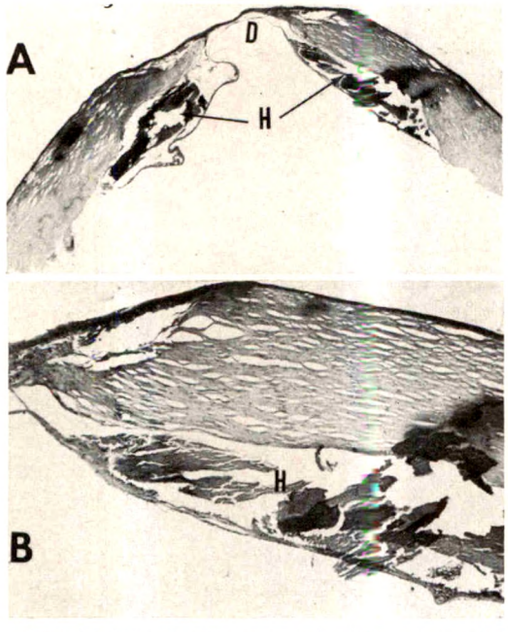



Fig. 14 (Kurz). Descemetocele (D), surrounded by deep intracorneal hematoma (H) (hematoxylin and eosin; top: ×15, bottom: ×48).

*Mooren's ulcer*—The only eye of a 75-year-old white woman slowly developed a marginal degeneration after lens extraction. In one year following surgery she had an advanced Mooren's ulcer encircling the cornea (Fig. 15), and vision was reduced to hand movements. An 11-mm lamellar keratoplasty was performed which became cloudy. The histopathology was characteristic of Mooren's ulcer with an overhanging central edge and epithelium from the periphery lining the necrotic ulcer bed (Fig. 16).

*Band keratopathy*—Nine years following lens extraction, a 62-year-old white woman

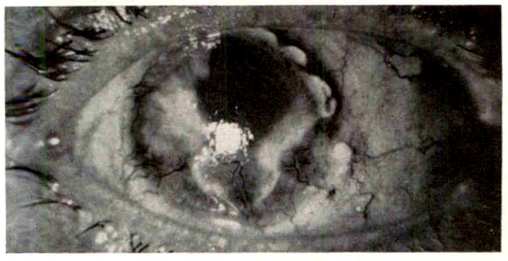


Fig. 15 (Kurz). Mooren's ulcer one year following lens extraction.

had a lamellar graft for band keratopathy (Fig. 17). Ten years prior to cataract surgery she had had a thyroidectomy followed by tetany. She had been maintained on calcium gluconate and vitamin D, but was found to be hypercalcemic 10 months prior to the corneal graft. Calcium levels improved after the calcium gluconate was discontinued.

Microscopic sections demonstrated large deposits of calcium beneath a thin epithelium (Fig. 18). In addition, there was a degenerative pannus in front of Bowman's membrane. This suggests that a factor of dystrophic calcification (deposition of lime in dead or degenerating tissues not dependent on increase in blood calcium) was present in addition to that of metastatic calcification[9] (precipitation of calcium salts in previously undamaged tissues due to an excess in circulating blood). Calcification was not present in the fellow eye which was also aphakic. The graft was moderately clear with no evidence of calcification four months postoperatively.

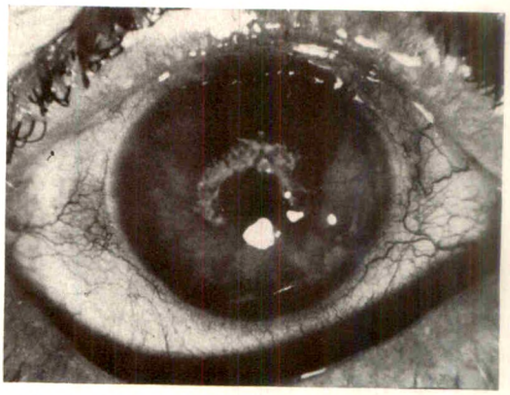


Fig. 17 (Kurz). Band keratopathy in 62-year-old aphakic patient who developed hypercalcemia. Note semicircular pattern of corneal deposits.

## Summary

Nine of 28 corneal graft specimens obtained following lens extraction exhibited a variety of unusual pathologic findings. The remaining 19, however, showed bullous keratopathy as the principal histopathologic finding. This was believed to be secondary to endothelial degeneration, demonstrable in all but the two lamellar specimens. Posterior excrescences on Descemet's membrane characteristic of endothelial dystrophy were absent.

Penetrating keratoplasty performed on 17 eyes with aphakic bullous keratopathy yielded satisfactory results in nearly half the cases during a follow-up period ranging from six months to four years. Considering the condition of the host endothelium, these

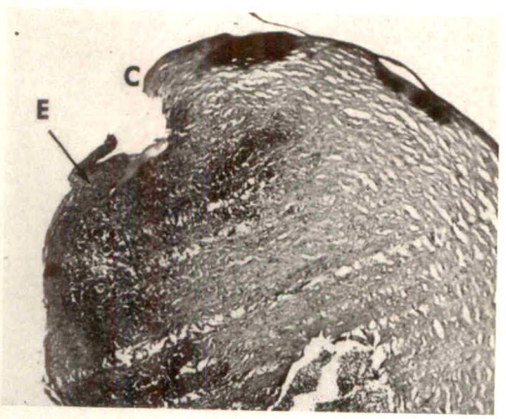



Fig. 16 (Kurz). Curved end of specimen shows bed of ulcer lined by epithelium (E). Note overhanging central edge (C) (hematoxylin and eosin, ×30).

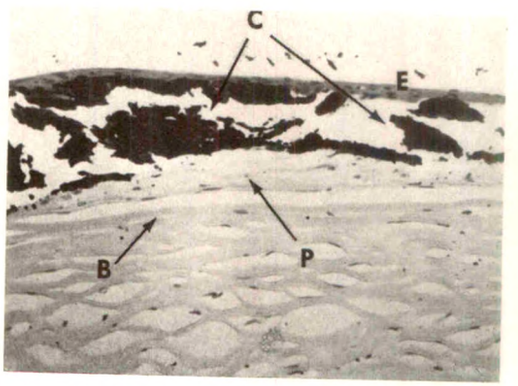



Fig. 18 (Kurz). Fragmented calcific deposit (C) between atrophic epithelium (E) and Bowman's membrane (B). A degenerative pannus (P) is present anterior to Bowman's membrane (von Kossa, ×120).

operative results are better than one might have expected.

A plea is made for persons doing corneal surgery to keep records of the ages of the donors.

ACKNOWLEDGMENTS

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OPHTHALMIC MINIATURE

"This is a very singular knife," said Holmes, lifting it up and examining it minutely. "I presume, as I see blood-stains upon it, that it is the one which was found in the dead man's grasp. Watson, this knife is surely in your line?"

"It is what we call a cataract knife," said I.

"I thought so. A very delicate blade devised for very delicate work."

"The tip was guarded by a disc of cork which we found beside his body," said the inspector. "His wife tells us that the knife had lain upon the dressing-table, and that he had picked it up as he left the room. It was a poor weapon, but perhaps the best that he could lay his hands on at the moment." . . .

. . . A knife which certainly no sane man would use for a weapon. It was, as Dr. Watson told us, a form of knife which is used for the most delicate operations known in surgery.

Sir Arthur Conan Doyle
*Silver Blaze*

# INFLUENCE OF VARIOUS AGENTS ON CORNEAL PERMEABILITY

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*Baltimore, Maryland*

There are some reports of the effect of a surfactant on corneal irritability[1,2] and enhancement of drug penetration into the eye,[3,4] but there is a paucity of detailed reports on the influence of agents on corneal permeability. The present study was undertaken to examine the effects of several agents on the permeability of the cornea to fluorescein, using an in vitro system.

## MATERIALS AND METHODS

Adult albino rabbits (2-3 kg) were killed with an overdose of sodium pentobarbital. Eyes were proptosed, the corneas removed and transferred immediately to a Petri dish containing Krebs-bicarbonate Ringer's solution (pH 7.2) at 23-24° C. Corneas were mounted in chambers described previously,[5] except that no simulated intraocular pressure was used. The inside volume (endothelial solution) of each chamber was 5 ml and corneas were always bathed with Ringer's solution on this surface.

Following mounting, the epithelium of a cornea was bathed with one of the following solutions for two minutes: $10^{-5}$ M histamine; 2% laboratory-prepared pilocarpine (JHHP); 2% commercially available pilocarpine HCl in half-strength Ringer's solution; 2 mM cetyl pyridinium chloride (CPC); 0.02%, 0.01% or 0.005% benzalconium chloride (BAC); 0.5% proxymetacaine (Ophthaine); 2% 1-norepinephrine; or $10^{-3}$ M ouabain. In addition to the two-minute exposure to $10^{-3}$ M ouabain, some corneas remained in ouabain for 30 minutes and some for two hours. One series of experiments was made using JHHP pilocarpine for two minutes followed by immersion in norepinephrine for two minutes before immersion in fluorescein for four minutes. All solutions, other than commercially available compounds, were made up in Ringer's solution, except as noted.

In order to bathe an exposed epithelium, the whole chamber was immersed in a large beaker containing sufficient solution to cover it. After the two-minute (or longer) exposure to a drug, the chamber was transferred to a beaker containing sufficient 5% sodium fluorescein (Fluorescite) to cover the exposed epithelium. After four minutes in fluorescein, the chamber was removed and carefully rinsed with distilled water to remove the excess fluorescein on the external chamber surface. Care was taken not to wash the top surface of the chamber or the epithelium. The chamber was then placed in a beaker containing sufficient Ringer's solution to cover the epithelium completely. Paired corneas were used in over 35% of all experiments. Both corneas in a pair were bathed in fluorescein and then immersed in Ringer's solution, but only one was previously treated with a drug.

After the epithelial surface was bathed in Ringer's solution the entire endothelial solution was removed and replaced at 30 and 60 minutes and finally removed at 120 minutes. These solutions were analyzed for fluorescein using an Aminco-Bowman spectrophotofluorometer. A linear relationship was found between the fluorescein concentration in Ringer's solution and the relative intensity (scale reading x sensitivity) below 0.1 mg%. Samples with a concentration close to this or

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higher were diluted with Ringer's solution before analysis. The apparatus was checked with known concentrations of fluorescein made in Ringer's solution before each determination was made of the samples. The analyses were thus made in essentially the same manner as described previously.[6]

A high pressure (80 cm water) applied to the posterior surface of the cornea causes a splitting of the superficial wing cells from the columnar basal cells which remain attached to the basement membrane.[7] To determine if the wing cell layer became more permeable, corneas were set up as previously described[7] with an 80 cm head of water on the posterior surface for one hour, except that the endothelium remained attached in the present experiments. At this time, the pressure was removed and the epithelial surface exposed to fluorescein for four minutes; the procedure then followed that described above for sampling of the endothelial solution.

Some corneas were mounted in other chambers[8] where small volumes of fluid bathed each corneal surface. The endothelium was always bathed in Ringer's solution. The epithelium was initially bathed in one of the following solutions for two minutes—0.2 or 2 mM lauryl sulfate (SLS) or 0.2 or 5 mM ethylenediaminetetraacetate (EDTA). The epithelial chamber was then flushed with 50 ml Ringer's solution and replaced with Ringer's containing $^{14}$C-mannitol. The endothelial bathing solution was sampled (total volume 3 ml; samples 20µl) every 30 minutes for two hours, and the epithelial solution was sampled at the beginning and end of the two-hour experimental period. The samples were counted using an end-window G-M tube. One cornea of each pair was treated as above while the other received no agent, but was treated identically, including flushing of the epithelial solution.

A few corneas were taken immediately after treatment with some agents, the exposed 6 mm diameter portion trephined out of the whole cornea and fixed in osmium for electron microscopy. The tissue was embedded in Araldite and sections were cut which were mounted on copper grids. The sections were stained with lead citrate and uranyl acetate and examined in an RCA electron microscope.

## Results

The amount of fluorescein passing the cornea per sampling period and the total amount in two hours is shown in Table 1. Although many experiments were made on paired corneas, the differences were so consistent that any permeability increase was readily obvious, thus all data are given in the respective groups.

Pressure applied to the posterior surface caused an increase in permeability; the epithelium is known to split longitudinally between the superficial and basal cells under high pressures,[7] and it is not surprising that it also produces some separation of the superficial epithelial cells where the principal resistance lies to the passage of water.[7] Figure 1 illustrates a normal epithelium from an untreated cornea. Figure 2 shows the effect of high pressure, where the principal effect is that of a widening of the intercellular spaces.

Corneas treated with ouabain ($10^{-3}$ M), were compared at two and 30 minutes when no increased permeability was found and at two hours, since an increase in corneal thickness occurs after two to three hours when ouabain is applied to the epithelial surface.[9,10] A 50-fold increase in dye penetration was found with two-hour ouabain. The intercellular spaces have become distended (Fig. 3) while the cells appear fairly normal. After 30-minute treatment with ouabain, the ultrastructure of the epithelium appeared normal.

Proxymetacaine, pilocarpine (JHHP), and the combination of pilocarpine (JHHP) and norepinephrine, all produced increased corneal permeability. Norepinephrine alone had no effect, nor did pilocarpine in Ringer's solution, eliminating these compounds from the possible agents causing increased permeability. The pH of the JHHP pilocarpine solu-

TABLE 1

AMOUNT OF FLUORESCEIN PASSING THE CORNEA PER SAMPLE TIME PERIOD AND TOTAL AMOUNT PASSING IN TWO HOURS

| Treatment | No. Corneas | Amount of Fluorescein Transferred (in $\mu$g ±SEM) | | | | Significance |
|---|---|---|---|---|---|---|
| | | 0–30 minutes | 30–60 minutes | 60–120 minutes | Total | |
| Ringer's solution alone | 26 | 0.107 ±0.022 | 0.208 ±0.035 | 0.204 ±0.033 | 0.505 ±0.070 | |
| Histamine $10^{-5}$ M | 3 | 0.050 ±0.033 | 0.082 ±0.038 | 0.137 ±0.035 | 0.270 ±0.103 | $0.4 < p < 0.3$ |
| Pressure 80 cm $H_2O$ | 5 | 0.433 ±0.059 | 2.097 ±1.126 | 0.683 ±0.168 | 3.077 ±1.089 | $p < .001$ |
| Ouabain $10^{-3}$ M (two minutes) | 4 | 0.093 ±0.021 | 0.166 ±0.073 | 0.150 ±0.085 | 0.371 ±0.095 | $0.5 < p < 0.4$ |
| Ouabain $10^{-3}$ M (30 minutes) | 4 | 0.027 ±0.010 | 0.023 ±0.012 | 0.045 ±0.010 | 0.095 ±0.022 | $0.005 < p < 0.02$ |
| Ouabain $10^{-3}$ M (two hours) | 4 | 11.393 ±2.394 | 9.380 ±1.868 | 4.445 ±0.644 | 25.218 ±4.615 | $p < .001$ |
| Proxymetacaine 0.5% | 7 | 0.566 ±0.316 | 0.854 ±0.257 | 0.747 ±0.136 | 2.167 ±0.692 | $p < .001$ |
| Pilocarpine 2% (JHHP) | 10 | 0.834 ±0.161 | 1.480 ±0.322 | 2.403 ±1.377 | 4.917 ±1.606 | $p < .001$ |
| Pilocarpine 2% (JHHP) and norepinephrine 2% | 4 | 0.340 ±0.183 | 0.717 ±0.186 | 1.041 ±0.174 | 2.097 ±0.492 | $p < .001$ |
| Norepinephrine 2% | 4 | 0.058 ±0.022 | 0.063 ±0.037 | 0.055 ±0.027 | 0.177 ±0.085 | $0.1 < p < .005$ |
| Pilocarpine HCl 2% in Ringer's solution | 4 | 0.048 ±0.009 | 0.167 ±0.020 | 0.144 ±0.019 | 0.359 ±0.041 | $0.5 < p < 0.4$ |
| BAC 0.005% | 4 | 0.364 ±0.182 | 1.064 ±0.377 | 0.828 ±0.328 | 2.256 ±0.750 | $p < .001$ |
| BAC 0.01% | 6 | 1.937 ±0.251 | 4.503 ±1.139 | 2.585 ±0.645 | 9.025 ±1.841 | $p < .001$ |
| BAC 0.02% | 3 | 2.595 ±1.083 | 6.085 ±1.107 | 3.885 ±0.894 | 12.565 ±2.985 | $p < .001$ |
| CPC 2 mM | 12 | 4.568 ±1.184 | 5.808 ±0.927 | 4.034 ±0.630 | 13.926 ±2.240 | $p < .001$ |

tion was pH 6.1 while that of the Ringer-pilocarpine solution was pH 6.4. All other solutions had a pH of 6.8-7.4, thus pH was without influence on corneal fluorescein permeability. Of all the components of the JHHP pilocarpine solution ($Na_2HPO_4$, $NaH_2PO_4$, NaCl, and BAC) and of the ophthalmic solution (Ophthaine) the only common compound was BAC. The concentration of BAC in proxymetacaine is 0.01% and in JHHP pilocarpine is 0.02%. BAC alone, at 0.02%, caused a 25-fold increase in permeability,

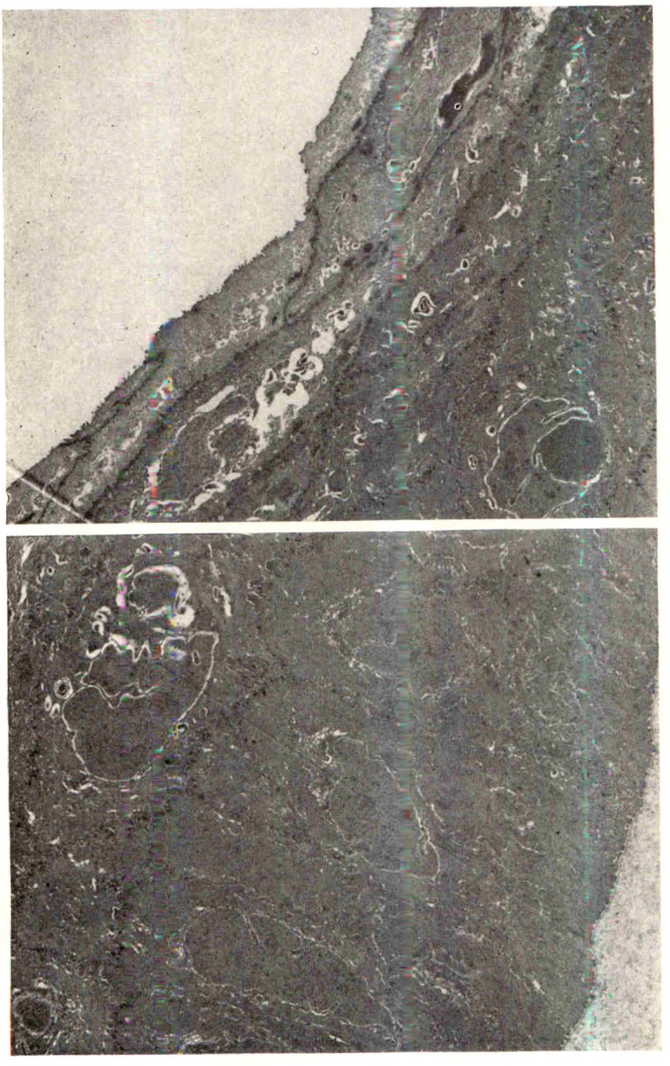


Fig. 1 (Green and Tonjum). Electron micrograph of epithelium from an untreated (control) cornea (×2640).

thus BAC alone had a greater effect than the equivalent concentration in a commercial preparation. Figure 4 shows the effect of 0.02% BAC; the superficial cells are disrupted and an increase in intercellular space is seen in the outer two or three cell layers.

The combination of JHHP pilocarpine followed by norepinephrine each applied for two minutes gives a three-fold permeability increase. The lower effect of this combination compared to the effect of JHHP pilocarpine alone may be caused by washing off the JHHP pilocarpine in the norepinephrine solution prior to immersion in fluorescein. The comparison between JHHP pilocarpine, the combined JHHP pilocarpine and norepinephrine, and BAC alone emphasized that BAC is the inducer of increased permeability.

Both BAC and CPC are cationic surfactants and they increased corneal fluorescein permeability; CPC (2 mM) caused a 30-fold increase. The superficial epithelium shows an increase in the width of the intercellular spaces after CPC treatment and the cell cytoplasm is slightly disrupted (Fig. 5). Increased intercellular spaces are found only in the superficial layers, with the basal cells showing a normal tight configuration. The anionic surfactant sodium lauryl sulfate

(SLS) had no effect on the permeability of the cornea to $^{14}$C-mannitol; neither did EDTA. No mannitol passed through the cornea under either control or experimental conditions.

Any agent which produced a permeability increase caused more fluorescein to pass out of the cornea in the 30-60 minute time period; the 0-30 minute sample was slightly lower (Table 1). The 60-120 minute sample generally showed a reduction in fluorescein transfer into the endothelial solution. When the total amount of fluorescein was very low, transfer was essentially the same for all time periods. This is expected since only a limited amount of fluorescein would enter the cornea and most of this would slowly diffuse into the endothelial solution.

## Discussion

Only $10^{-3}$ M ouabain (two-hours incubation), BAC, CPC, and high, posteriorly-applied hydrostatic pressure produced an increase in corneal permeability to fluorescein or mannitol. Both Ophthaine and JHHP pilocarpine increased permeability, but it was shown that BAC is the only common inducer of increased permeability in each solution. BAC in Ringer's solution produced a larger increase in permeability than the same con-



Fig. 2 (Green and Tonjum). Electron micrograph of superficial epithelium following high posteriorly applied pressure to the whole cornea. Notice the enlarged intercellular spaces (×30,044).

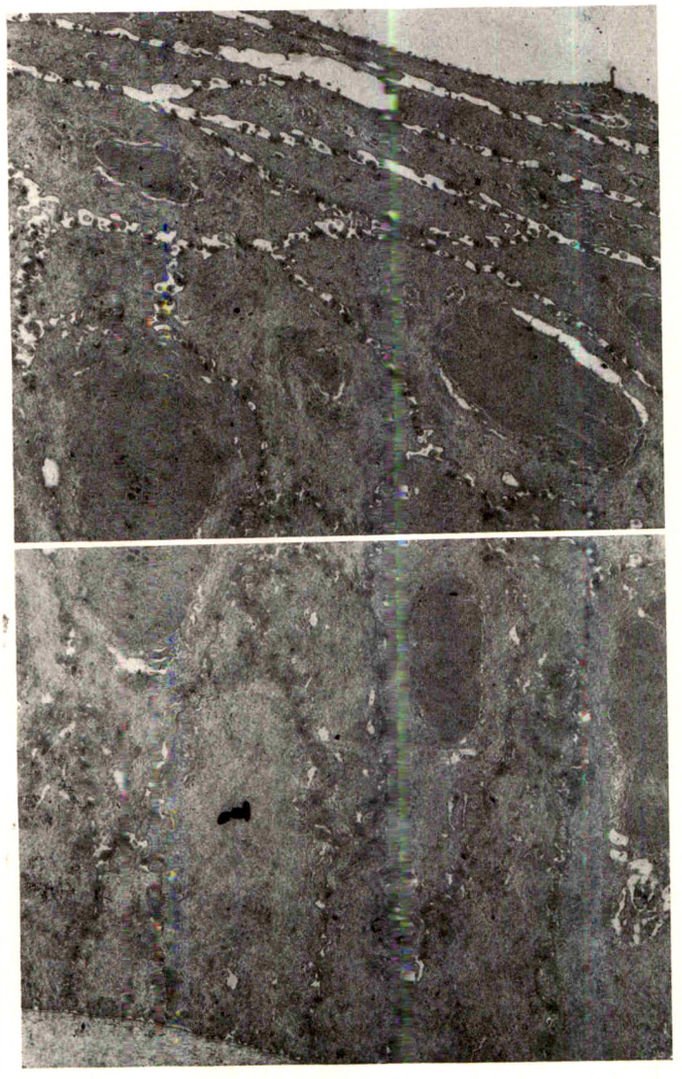


Fig. 3 (Green and Tonjum). Epithelium of a cornea treated with $10^{-3}$ M ouabain for two hours on the epithelial surface. Enlargement of intercellular spaces through the whole epithelium is obvious, with larger spaces in the superficial layers. Some intracellular disturbance is evident (×2640).

centration in commercial products. The differences seen here between BAC in Ringer's solution and BAC in commercial products (at the same percent of concentration) may reflect either differences in molecular weight, or differences between batches of the commercial products.

Ouabain inhibits cellular active transport systems[11] and causes increased corneal thickness when perfused over the epithelial surface.[9,10,12] It has been reported that two-hour incubation in ouabain at $10^{-3}$ M has no effect on the permeability of the corneal endothelium to urea or sucrose.[13] Here, a highly significant increase in epithelial fluorescein permeability is seen after two-hour incubation.

Electron microscope findings show that posteriorly applied pressure produced a breakdown in the cohesion of the epithelium (Fig. 2) by increasing the width of the intercellular space. Ouabain (Fig. 3), BAC (Fig. 4, and CPC (Fig. 5) all produced some disruption of the cell cytoplasm presumably either by actions on the plasma cell membrane per se (BAC and CPC) or on the intracellular metabolism (ouabain). The cationic surfactants, BAC and CPC, together with ouabain, produced an increase in the width of the intercellular space of the superficial epi-

thelial cells, indicating that they affect not only the cell membrane but also the intercellular route. The effects on the intercellular space are more pronounced in the region of the superficial epithelium when compared to the basal epithelial cells; only in the case of high, posteriorly applied pressure[7] and ouabain treatment does the widening of the intercellular spaces extend to the basal cell layers.[14]

BAC has been shown to be an effective antiseptic at concentrations of lower than 1 in 2,000 (0.05%)[15-17] and it is widely used in different concentrations (0.02% to 0.004%) as a germicide in topical ophthalmic solutions. Swan[1] and O'Brien and Swan[18] reported that BAC concentrations of 0.04-0.05% produced punctate epithelial disturbances which recover spontaneously when the drug is discontinued: BAC concentrations of 0.02-0.03% had no effect on the epithelium. Further, it has been shown that instillation of a 0.025% solution of BAC into the eye every day for 10 days produced no gross injury or thickening of the anterior epithelium.[19] Topically applied BAC (0.005 M), however, produced a loosening in adhesion between the corneal epithelium and



Fig. 4 (Green and Tonjum). Effect of 0.02% BAC on the corneal epithelium. Note the enlarged intercellular spaces between the superficial cells. Note also the cytoplasmic disruption in the most superficial cell layer (×2640).



Fig. 5 (Green and Tonjum). Effect of CPC on the superficial corneal epithelium. There is a much greater disruption of the cytoplasm than seen after BAC. An increase in the width of the intercellular space is seen when compared to the normal (Fig. 1); note that the areas where desmosomes are present remain closely apposed (×16,650).

stroma.[20] BAC is known to increase the permeability of another epithelial membrane, namely frog skin,[21] and the effect of related compounds (such as CPC and SLS) was shown to be on the passive permeability of the membrane.[22]

Neither histamine nor norepinephrine caused increased permeability, although it has been reported that these agents cause a loosening of the epithelium.[14] The incubation time in these latter experiments, however, was 20 hours so it is not surprising that two-minute incubation was ineffective.

The wide use of benzalconium chloride (Zephiran) as an antiseptic might suggest that it is an inactive compound regarding permeability, but the present results, together with previous investigations,[3,4,18,23] show that BAC can increase corneal permeability. Since most drugs penetrate the cornea only very slowly, the inclusion of an agent such as BAC, which produces a permeability increase, would be advantageous. Indeed, when describing the intraocular effect of topically applied drugs (in particular, water soluble ones), it may well be that the same drug in different preparations (with different concentrations of BAC) produces different effects and it would appear to be worthwhile to take into account the BAC

concentration of the solution, since higher concentrations would increase drug penetration.

Marsh and Maurice[24] recently reported on the effects of non-ionic detergents on human corneal permeability to fluorescein and concluded that there was a narrow margin between increased permeability and the creation of discomfort and epithelial disturbance. Such a conclusion also appears applicable to BAC, as shown above. Swan[1] reported, however, that the minimal concentrations of wetting agents producing irritation in the conjunctival sac are greater than those that are effective therapeutically as germicides.

## Summary

Corneal fluorescein permeability has been measured following treatment with different agents. Ouabain ($10^{-3}$ M for two hours), proxymetacaine (Ophthaine), and commercial pilocarpine (two-minute incubation) increased fluorescein transfer; pilocarpine in Ringer's solution did not. The active component of the commercial products was benzalconium chloride (Zephiran); dilute solutions of benzalconium chloride (a cationic surfactant) in Ringer's solution increased fluorescein permeability. Another cationic surfactant, cetyl pyridinium chloride, was similarly effective. Posteriorly applied pressure, ouabain and the surfactants increased permeability due to widening of intercellular spaces.

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# INCORPORATION OF RADIOACTIVE SULPHATE BY CORNEAL STROMA DURING CRYOPRESERVATION

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Adequate cyropreservation of corneal tissue for penetrating keratoplasty requires the survival of corneal endothelium. Experimental[1-5] and clinical data[6-7] support the importance of this corneal layer in the success of full-thickness grafts. The ability of nonviable corneal stroma to become transparent when a semipermeable membrane is placed instead of the endothelium[8,9] demonstrates the relative importance of corneal connective tissue cells (or keratocytes) in corneal transparency. This was observed in a previous study in which grafts of cryopreserved rabbit corneas remained clear from the day of transplantation even though there was histologic and historadiographic evidence of lack of keratocyte survival.[3] There is clinical evidence also that lamellar grafts with nonviable tissue are clear before the graft is repopulated by keratocytes.

The incorporation of radiotagged sulfate ($^{35}S$) in connective tissue depends on the viability of its cell population and their ability to synthesize ground substance. Other factors, such as edema, may decrease the uptake, thus suggesting poor cell survival or cell death.[10] However, under controlled conditions this technique is valuable in assessing stromal cell viability.

In the experiments reported here, we investigated the feasibility of increasing the survival of corneal stromal cells during cryopreservation; this was determined by their ability, in vitro, to incorporate $^{35}S$-labeled sodium sulfate.

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## MATERIALS AND METHODS

Adult albino rabbits were killed with intravenous pentobarbital and their eyes enucleated. The corneas were promptly removed and treated with a solution of dimethylsulfoxide (DMSO), sucrose, and rabbit serum following freezing procedures previously described.[6,11]

*Group 1*—Two corneas were placed in the controlled-rate freezer (CRF) which had been precooled to 4° C. The freezing cycle was initiated at a speed of 2°/minute. When the eutectic point (plateau) for this tissue and its preserving medium appeared (−10° C), the freezing rate was accelerated to 5°/minute until −80° C was reached. The corneas were then transferred to a liquid nitrogen storage tank at −180° C.

In order to determine the optimum freezing rate, we experimented with increasing the freezing rates after various temperatures had been reached at a rate of 2°/minute. For example, in Group 2, the rate of freezing was 2°/minute until −20° C was reached, at which point the rate was accelerated to 5°/minute. For the third group, the rate was increased from 2° to 5°/minute at −30° C. Acceleration was begun at −40°, −50°, and −60° C in Groups 4, 5, and 6, with two corneas used in each group. Tissues were stored for periods of one to six days.

Corneas were thawed by immersing their glass vial containers in a 65° C water bath for 50 seconds. To remove the dimethylsulfoxide, they were then transferred to a beaker containing calf serum, where they remained for two hours at room temperature.

*Incorporation of radiotagged sulphate*—Corneas from each freezing experiment, plus a fresh cornea, were incubated at 37° C for two hours in calf serum with 100 mc/ml sodium sulfate (sp. activity 100 mc/mM,

New England Nuclear Corp.). The solution was gently agitated every 15 minutes.

Following incubation, the corneas were washed in normal saline, incubated in a saturated solution of sodium sulfate at 37° C for two hours with frequent agitation. The solution was changed and the corneas refrigerated overnight at 4° C. After repeated agitations, the corneas were rinsed through several changes of distilled water and placed in a 50% alcohol solution for one hour for partial dehydration. The corneas were dried flat between strips of filter paper in an incubator at 37° C for 48 hours, and contact radioautographs were made on Kodak radioautographic plates (no screen) with an exposure time of 11•days. Plates were developed in Dektol 1/1.

## Results

*Evaluation of results*—Maximum incorporation of $^{35}S$ as shown in radioautographs was rated four plus (4+). Less uptake was rated from 3+ to 0, according to the density of the radioautographs. The results are summarized in Table 1. Maximum uptake of $^{35}S$ was observed in fresh corneas, while no uptake was shown in radioautographs of corneas frozen without DMSO. A small amount of uptake (1+ and 2+, respectively) was present in corneas with a freezing rate accelerated to 5°C/minute at −10° and −20° C. The isotope incorporation improved at −30° C when it was close to that of the fresh cornea (3+). Somewhat less uptake (2+) was present when acceleration began at −40° C, and little uptake occurred (1+) in corneas whose freezing rate was modified at −50° and −60° C.

TABLE 1

RATE OF $^{35}S$ UPTAKE AND STROMAL CELL SURVIVAL AT VARIOUS FREEZING SPEEDS

| Temperature at which Freezing Rate was Accelerated (in degrees C) | Rate of $^{35}S$ Uptake by Stromal Tissue | Rate of Stroma Survival |
|---|---|---|
| −10 | + | + |
| −20 | ++ | ++ |
| −30 | +++ | ++++ |
| −40 | ++ | ++ |
| −50 | + | + |
| −60 | + | + |

After autoradiography was completed, one cornea from each group was fixed in 10% Formalin and washed. Tangential frozen sections were made to study cell population in sections stained with hematoxylin-eosin. Cell-population was compared to that of sections of fresh corneas and rated from one to four plus. The decrease in number of stained stromal cells, or their complete absence, correlated well with diminished uptake of $^{35}S$.

## Comment

These experiments demonstrate that the survival of rabbit corneal stromal cells in tissue previously treated with a cryophylactic solution containing DMSO can be modified by altering the rate of freezing. Even though different cell populations may require different freezing rates for optimal survival, it is believed that most cells will preserve well with a freezing rate varying between 2° and 5° C/minute.[12] In the case of corneal endothelium, the best preservation is obtained with an initial rate of 2° C/minute, increased to 5° C/minute after the eutectic point is attained.[6,11] The corneal epithelium seems to survive at the same freezing rate, and the slight $^{35}S$ uptake shown by corneal stroma when this freezing rate is used suggests that some stromal cells immediately below the endothelium and epithelium may also survive.[3] Stromal cell survival was also noted in previous studies in which oxygen consumption was measured from the endothelium and the underlying stromal tissue of cryopreserved corneas.[13]

The improvement in stromal cell viability with a freezing rate of 2° C/minute past the eutectic point (to −30° C) suggests that a prolonged period of time is required for the central corneal layers to participate in the slower freezing rate. Unfortunately, we were unable to obtain radioautographs of

cross-sections of these corneas to substantiate this theory, since the whole-mount radioautographs indicate only total uptake.

Corneas not treated with a cryophylactic solution showed no uptake of sulfate, and no cells were seen in stained sections. Except in situations in which the host tissue has very poor regenerative ability (areas of necrosis or old corneal disease), corneas frozen without preservative become non-viable material adequate for lamellar keratoplasty or tectonic grafts for keratoprosthesis. It is possible that pretreatment with DMSO may permit survival of a large stromal cell population and improve the viability of corneas frozen in regular laboratory freezers for lamellar keratoplasty. Since cardiovascular and ear surgery often calls for vein homografts, the value of cryopreservation of connective tissue is not necessarily limited to the cornea. Our experiments suggest that freezing curves similar to those applied to corneal tissue can be correlated to segments of veins with the advantage of long-term tissue storage or true banking. Since previous studies have shown that the antigenicity of frozen (non-viable) or cryopreserved tissue does not depend on its viability,[14,15] a persistence of tissue antigenicity because of preservation of its cellular elements is most likely unimportant.

## Summary

Experiments were carried out to determine the optimal freezing rate for corneal stroma preservation. This was assayed by histology and by assay of the incorporation of radioactive sulfate in tissue samples frozen at various rates of speed. Rabbit corneas were treated with dimethylsulfoxide and frozen at rates of 2°/minute and this rate was accelerated to 5°/minute when various freezing points were reached. The best preservation was obtained by maintaining a rate of 2° C/minute until the temperature reached −30° C, when the freezing rate was increased to 5° C/minute until −80° C was reached. A similar freezing rate is suggested for vascular tissue.

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# HISTOLOGIC AND ELECTRON MICROSCOPE STUDIES OF LIGNEOUS CONJUNCTIVITIS

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Repeated bacteriologic, histologic,[1] and electron microscopic[2,3] studies have failed to clarify the etiology of ligneous conjunctivitis. However, recent histochemical investigations by François and Victoria[4] demonstrated that, in ligneous conjunctivitis, acid mucopolysaccharides collect in great amounts around newly formed vessels.

Our histochemical and electron microscopic studies of a case of ligneous conjunctivitis demonstrates that areas with staining characteristics of acid mucopolysaccharides have the appearance of a multilayered basement membrane-like material. This material is located around new vessels and forms the bulk of the growth.

## CASE REPORT

An otherwise healthy 14-year-old boy was seen for the first time with a 10-month history of a small indurated mass under the right upper eyelid. This lesion was excised twice, but recurred to become as large or larger in size. His visual acuity was 20/20 in both eyes without correction.

On external examination, the right eye was normal except for a slight thickening of the temporal upper eyelid. There was abundant mucoid secretion in the right conjunctival cul-de-sac and mucous strands were present over the right cornea. The right lower eyelid was normal as were the cornea and tranparent media. Eversion of the upper eyelid showed a flattened, pedunculated mass with a whitish pseudomembrane (Fig. 1). The base of the growth was heavily vascularized and bled when touched lightly with a small forcep. The rest of the conjunctiva showed mild follicular reaction. Only the most superficial layers of the thick pseudomembrane could be removed without bleeding.

A biopsy excision of this growth was performed. Hyaluronidase drops (500 units/ml) and alpha-chymotrypsin (1/5,000) were prescribed every two hours, but neither these treatments nor subsequent hyaluronidase injections into the area of excision, and cryocauterization, served to inhibit the growth. Corticosteroid therapy, however, reduced the amount of secretion. For the past 12 months, the patient elected to discontinue these treatments. Peripheral corneal vascularization and upper corneal erosions developed, but were successfully treated with a hydrophilic contact lens.

## HISTOLOGY

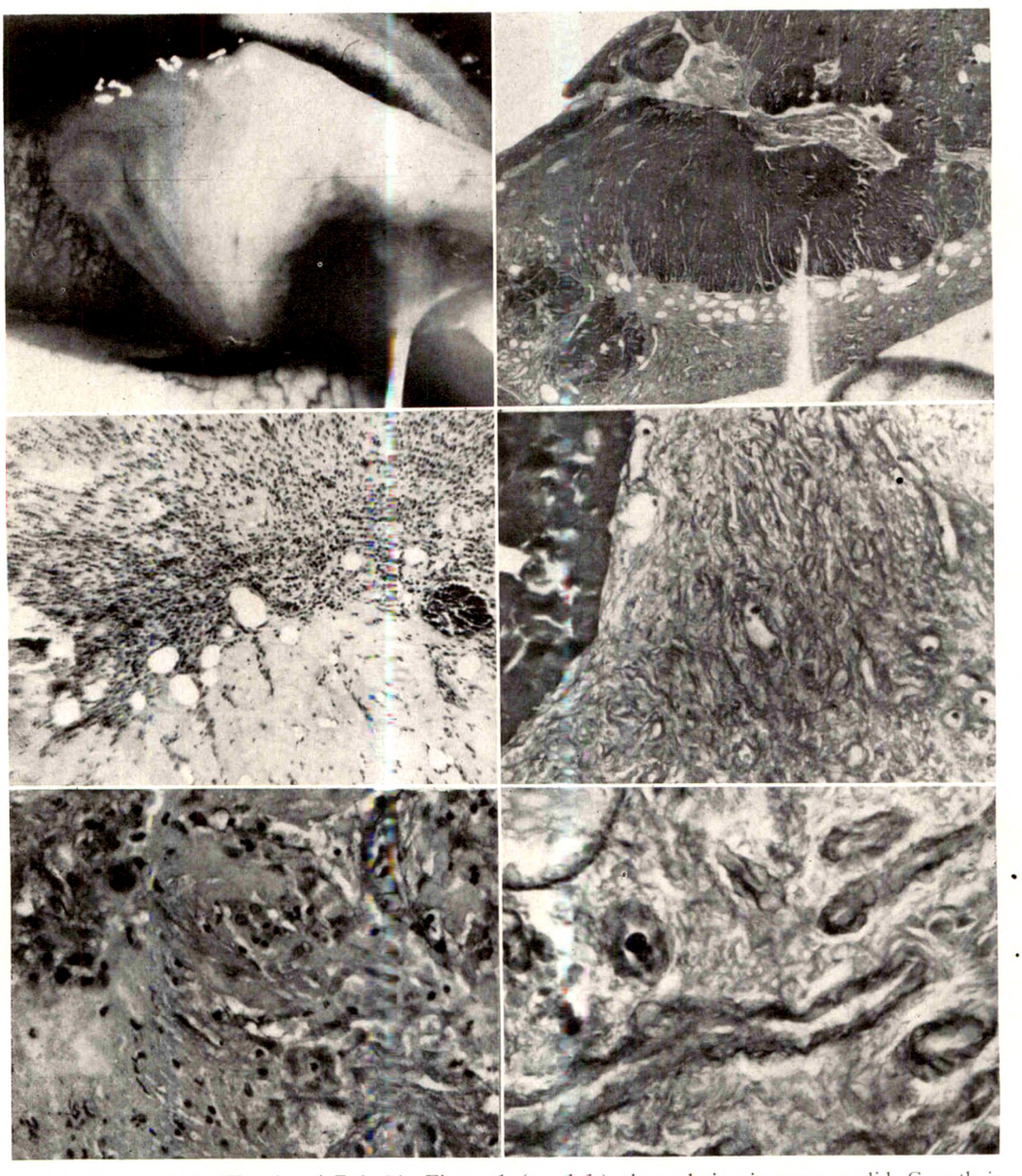
A cross-section of the specimen stained with PAS showed a dense amorphous deposit covered by a pseudomembrane (Fig. 2). The amorphous mass stained deeply red with PAS stain and had a vascular core from which many fine capillaries advanced throughout the tissue. Sections stained with hematoxylin and eosin showed multiple areas of round cell infiltration around capillaries in the deep portion of the biopsy as well as some multinucleated cells (Fig. 3). Polymorphonuclear leukocytes and few eosinophiles were present in the external portion and in the pseudomembrane. Part of the tissue was relatively avascular, but in some areas there was a profuse bed of fine capillaries surrounded by PAS positive material (Fig. 4) and alcian-blue staining material (Fig. 5). Examination of PAS-stained sections under high power showed deposition of mucopolysaccharide material which was hyaluronidase-sensitive around and between capillaries (Fig. 6). Stains for reticulin demonstrated a net of argyrophillic fibers in these areas.

The portion corresponding to the pseudomembrane was weakly eosinophilic. A few epithelial cells, lymphocytes, and polymorphonuclear leukocytes were present within the fibrinous layer. Biopsies taken after treatment with hyaluronidase showed a similar structure.

Specimens for electron microscopy were immediately fixed. After two hours in cold 2% osmium tetroxide with phosphate buffer,

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Figs. 1 through 6 (Kanai and Polack). Figure 1 (top left) shows lesion in upper eyelid. Growth is covered by a thick tenacious fibrinous pseudomembrane. Figure 2 (top right): Low-power view of biopsy specimen sectioned towards its base. It shows a dense PAS staining area with a central net of vessels. Clefts and empty capillaries separate the bulk of the tissue from its surface (PAS stain, ×4.5). Figure 3 (center left): A dense round cell infiltration was present in some areas. These were mostly lymphocytes. An eosinophilic homogeneous material (below) bonds to PAS positive areas (hematoxylin-eosin, ×100). Figure 4 (center right): Areas around the between capillaries stain with PAS (PAS stain ×200). Figure 5 (bottom left): Stroma of specimen showing positive staining for acid mucopolysaccharides (alcian blue, ×200). Figure 6 (bottom right): High power view of PAS staining material around capillaries. A similar area was studied by electron microscopy (PAS—alcian blue, ×400).

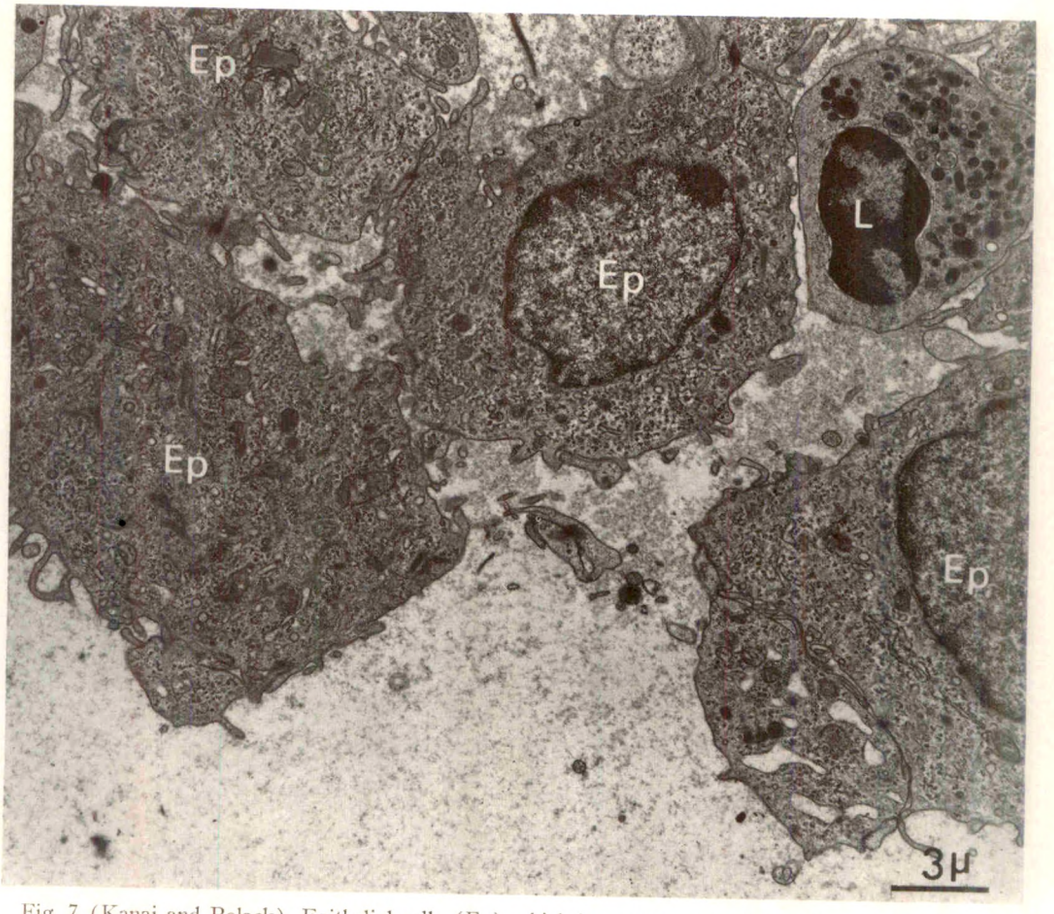



Fig. 7 (Kanai and Polack). Epithelial cells (Ep) which have many processes and are only attached by desmosomes are present in the pseudomembrane. Leukocytes (L) are interposed between epithelial cells (×4600).

they were dehydrated through a series of ethyl alcohol treatments and embedded in Epon. Thick sections were stained with toluidine blue and studied with the light microscope for orientation in electron microscopy. Embedded tissue was cut with a Porter-Blum microtome and stained with uranyl acetate and lead citrate.

Electron microphotographs were taken with a Hitachi 11-C microscope. The amorphous substance which characterized the superficial portion of this tissue was partially covered by epithelial cells and contained leukocytes and fragmented cells (Fig. 7). Epithelial cells formed two to four layers, were usually rounded with many processes, and attached only by desmosomes. The epithelial cell membrane facing the stroma had multiple projections and showed a basement membrane; however, this was absent in some areas. Several layers of fibroblastic cells were located immediately under the epithelial cells.

Lymphocytes, plasma cells, monocytes, free red cells, fibroblasts, capillaries, and a few bundles of fibrillar material were present in the stromal portion of the specimen (Fig. 8). Fibroblasts showed distended endoplasmic reticulum containing a thinly dispersed flocculent material. Bundles of fine filaments were seen in the center or periphery of the cells with a well developed Golgi complex (Fig. 9). Fibrillar materials, with or without banding, were found in the

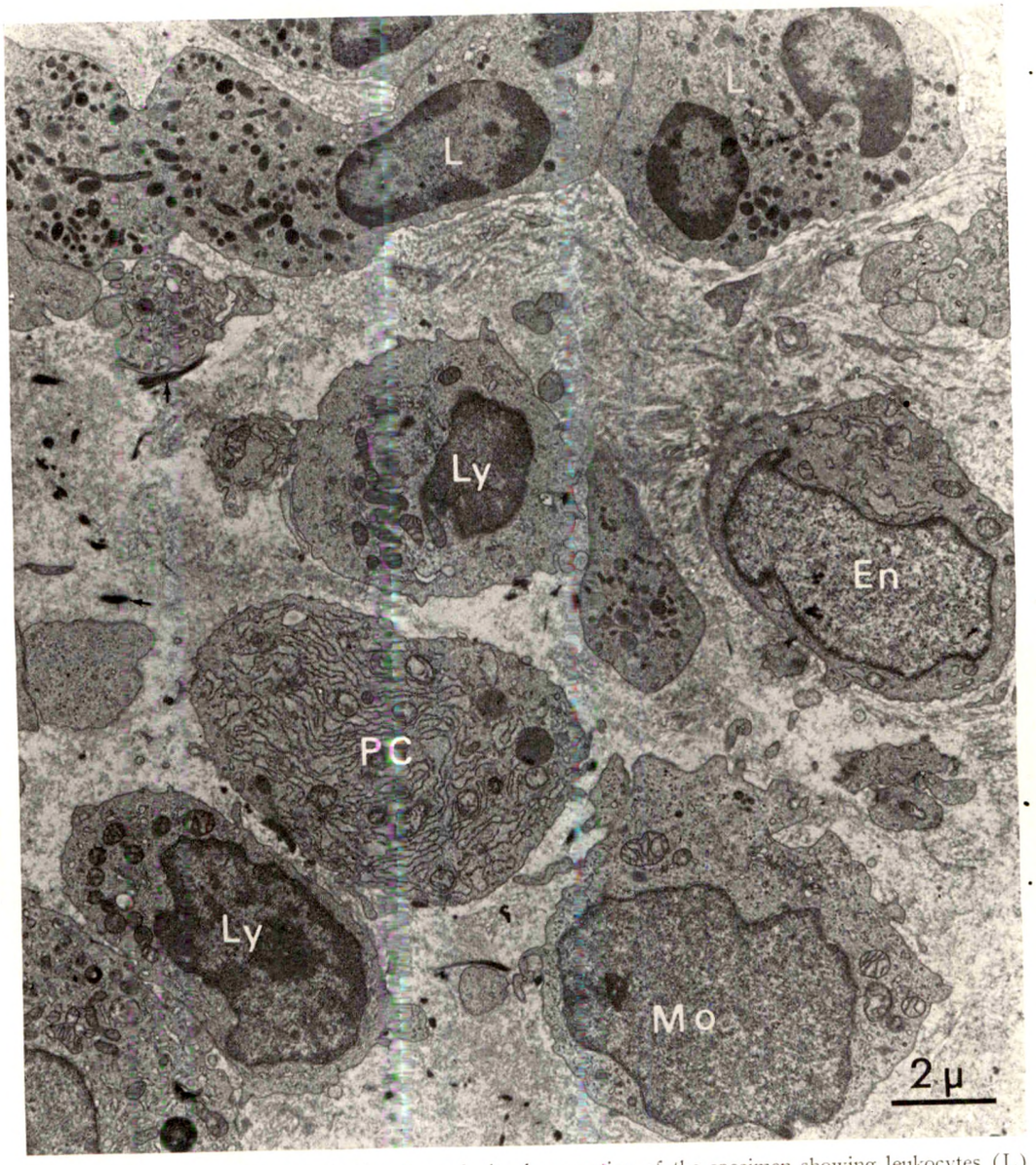



Fig. 8 (Kanai and Polack). Section through the deep portion of the specimen showing leukocytes (L) a free endothelial cell (En), a small bundle of fibrillar material (arrow) lymphocyte (Ly), monocyte (Mo), and plasma cell (Pl) (×7000).

stroma (20 nm). Occasionally, typical collagen fibers could be seen between these fibers.

Capillary endothelial cells had many cytoplasmic projections and were attached by tight junctions near the lumen. Vascular endothelial cells were usually wide around the nucleus; their cytoplasm contained mitochondria, distended endoplasmic reticulum, pinocytotic vesicles, and few inclusion bodies. Capillaries were surrounded by several lamellae of basement membrane-like material (Fig. 10) with a homogenous structure and irregular thickness (70-200 nm). Often, leukocytes were found within the layers of thick lamelliform formations (Fig. 11). Homogenous substances of higher density than the basement membrane formation were frequently found (Fig. 12).

## Discussion

Ligneous conjunctivitis is a rare disease of children and young adults which begins as a unilateral pseudomembranous conjunctivitis affecting one or both eyelids; this is eventually followed by an indurated growth. The disease runs a chronic course[5] and seems to be resistant to most kinds of treatment. François and Victoria[4] recently reported a favorable response to topical alpha chymotrypsin and hyaluronidase. The case presented here, however, did not respond to this treatment.

The most characteristic histologic findings are neovascularization, deposits of fibrillar material, and alcian-blue or PAS-positive staining materials around and between capillaries. Electron microscopic studies show a filamentous or homogenous material of irregular thickness arranged in multilayers around vessel walls. The density of PAS-positive areas forming the bulk of the specimen is similar to the perivascular homogenous material present around capillaries, suggesting a common vascular origin.

Thickening and reduplication of basement membranes occurs in diabetes mellitus and is found in retinal capillaries,[8] capillaries of subcutaneous tissue,[9] muscle,[10] kidney,[11] and

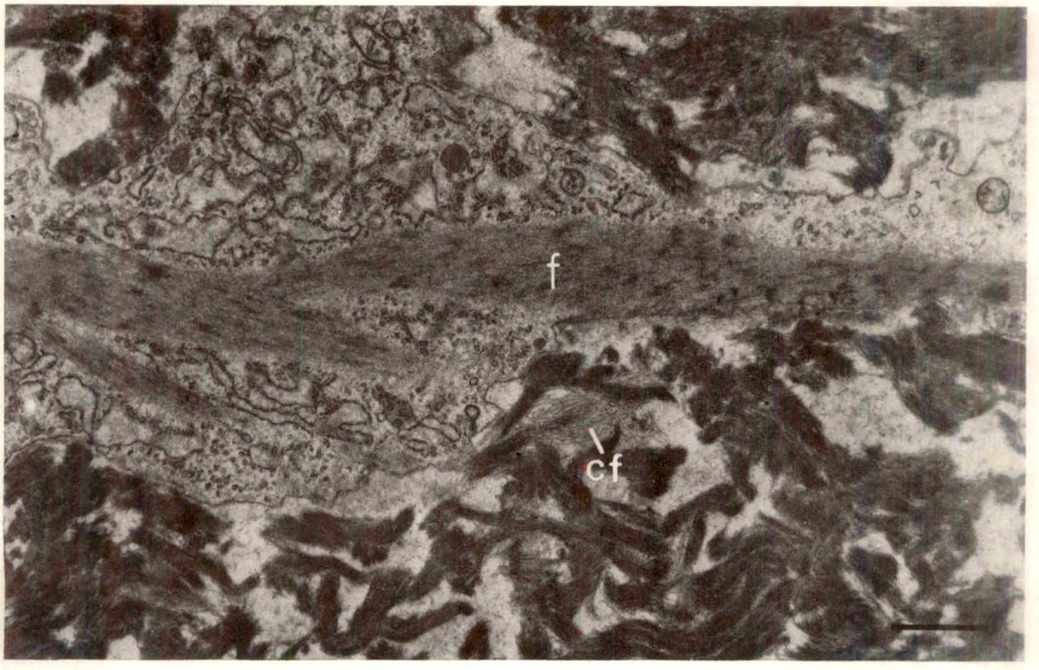



Fig. 9 (Kanai and Polack). Fibroclast (f) has sacs of distended endoplasmic reticulum. Bundles of fine filaments can be seen in the cytoplasm and outside the cell (×13,000).

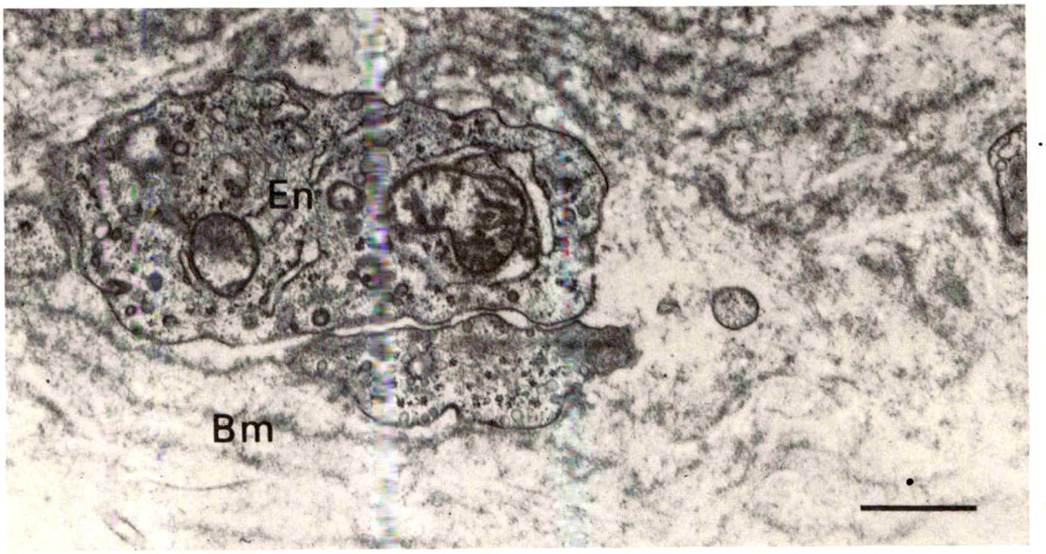



Fig. 10 (Kanai and Polack). Capillary with lamelliform basement membrane-like material (Bm) around its wall. En = endothelium (×16,000).

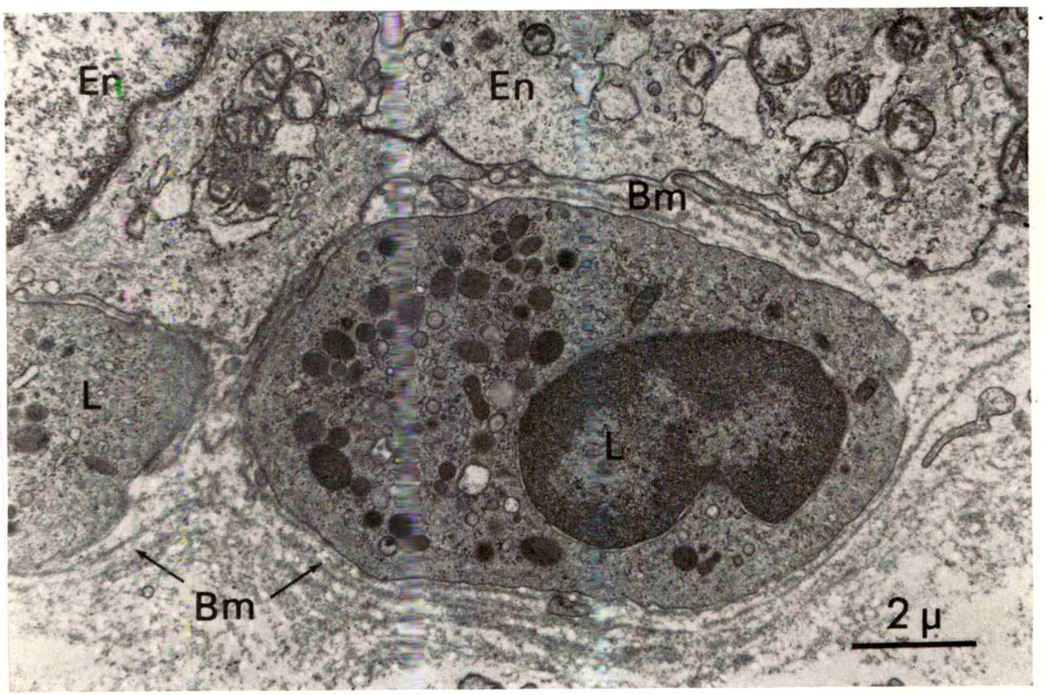



Fig. 11 (Kanai and Polack). Leukocytes (L) are seen surrounding the layers of the basement membrane-like materials (Bm) (×8200).

also in conjunctival capillaries.[12,13] This so-called lamelliform thickening of basement membrane is due to deposition of mucopolysaccharides and glycoproteins which stain with alcian-blue and PAS.[8] The basement membrane of normal vascular conjunctival endothelium consists of one or several layers, 50 to 100 nm thick, running nearly parallel to the outer contour of endothelial cells. Sometimes this membrane shows fenestrations.[14] The capillary endothelium observed in this case showed no fenestrations but had a lamelliform basement membrane-like formation. The relation between PAS or alcian-blue positive material and the basement membrane-like material was not previously described in ligneous conjunctivitis.

The lamelliform basement membrane-like material may derive either from the blood or be elaborated by the endothelial cell. The first possibility may be supported by the observations of Pappas and Tennyson,[15] who reported that marker particles passed from the lumen to the surrounding connective tissue of inflamed ciliary processes through thick capillary endothelium rather than through attenuated and fenestrated endothelial walls. In diabetes, Tamura[12] suggested that capillaries, because of an altered basement membrane, have an increased permeability to some materials. The second possibility may be supported by Curran's observations;[16] he reported that vascular endothelium produces mucopolysaccharides, and this activity is greatly increased in pathologic material such as in areas of wound healing or in stroma of tumors. It seems possible that in ligneous conjunctivitis, serofibrinous transudate may subsequently undergo coagulation, with the resultant formation of granulation tissue and hyaline material. With the electron microscope these hyaline deposits correspond to banded fibrils with a periodicity of 20 nm. Therefore, the hard ligneous consistency of this pathologic tissue may originate in direct outpouring of fibrin from neovessels and by passage of, or elaboration of, mucopolysaccharides by endothelial cells. In vitro studies with radiotagged sulfate ($^{35}S$) may elucidate whether these endothelial vessels are able to synthetize sulfated material.

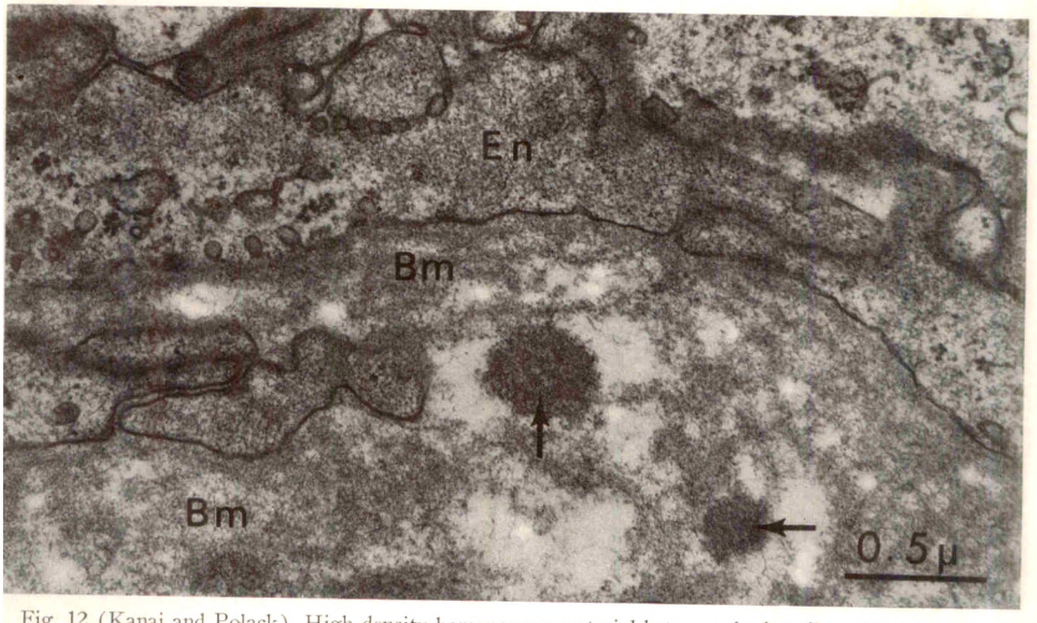



Fig. 12 (Kanai and Polack). High-density homogenous material between the lamellae of basement membrane-like material (arrows) (×38,000).

## Summary

Histochemical and histologic examination of a specimen of ligneous conjunctivitis revealed deposition of acid mucopolysaccharide, neovascularization, and round-cell infiltration. Areas of alcian blue-PAS positive deposits around capillary walls correspond to ultramicroscopic multilayered basement membrane-like material which forms the bulk of the growth. It is suggested that such material may be the result of increased capillary permeability, or it may be elaborated by endothelial cells, or both.



## Acknowledgments

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# ATYPICAL BAND KERATOPATHY IN GLAUCOMATOUS PATIENTS

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This report is to call attention to a keratopathy observed in well-controlled primary glaucoma patients, usually on long-term miotic therapy. Since 1963, 18 patients were observed who have manifested this clinical picture.

It is characterized by changes resembling band keratopathy, but having a different distribution pattern, usually paracentral in the interpalpebral area, over the lower central and nasal portion of the cornea, becoming less pronounced toward the periphery (Fig. 1). Clinically, fine, grayish, granular deposits can be seen in the paracentral areas in the subepithelial layers of the cornea. As the deposition increases, it tends to extend toward the limbus horizontally. Separate small areas may coalesce and progress in size and density rapidly, over a few months, or in a year or two. Rounded or irregular clear areas may develop in the opacified zone. Encroachment over the pupillary area may result in severe reduction in vision. Other symptoms may include photophobia, lacrimation, and irritation, because the overlying epithelium may become slightly roughened. The corneas have intact sensitivity and are not vascularized. Schirmer's tear function test was normal in the 10 patients who were studied.

The distribution of these corneal changes in our 18 patients has been diagrammed (Fig. 2). Ten of the patients were men and eight were women. They ranged in age from 64 to 87 years with the average age being 75 years.

The keratopathy appeared as a bilateral manifestation in 14, all of whom were being treated with miotics bilaterally. In three, only one eye was treated with miotics and the keratopathy developed only in that eye. In the one other patient, miotics were being used in both eyes, but the keratopathy developed in only one eye. It has been noted, however, that the changes in one eye may precede the other by as long as four years, so this patient may still develop bilateral involvement.

With two exceptions, duration of miotic therapy ranged from six to 16 years before the appearance of the keratopathy. In two patients, it occurred in less than one year (seven months in one and eight months in the other). Sixteen of the patients had wide-angle glaucoma, while two had a narrow-angle mechanism.

The incidence of this atypical band keratopathy must be low; its occurence is noted infrequently in the general glaucoma population, and in the practices of seven ophthal-

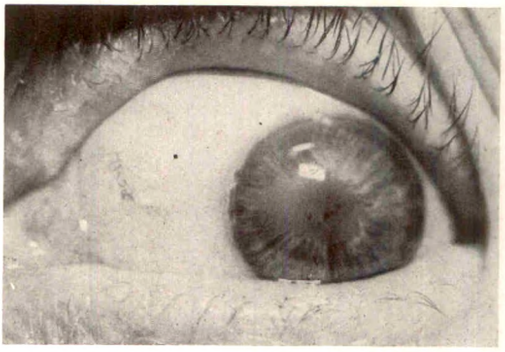


Fig. 1 (Kennedy, Roca, and Landers). Characteristic clinical picture of atypical band keratopathy in patient on long-term miotic therapy.

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Fig. 3 (Kennedy, Roca, and Landers). Patient 1. Top: Bilateral keratopathy. Bottom: Clear corneas bilaterally after EDTA treatment. Left eye shows slight residual temporally.

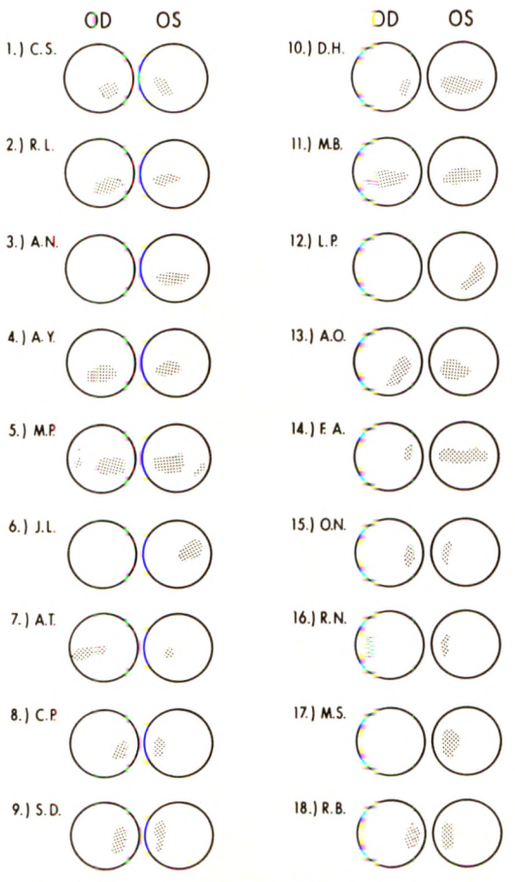


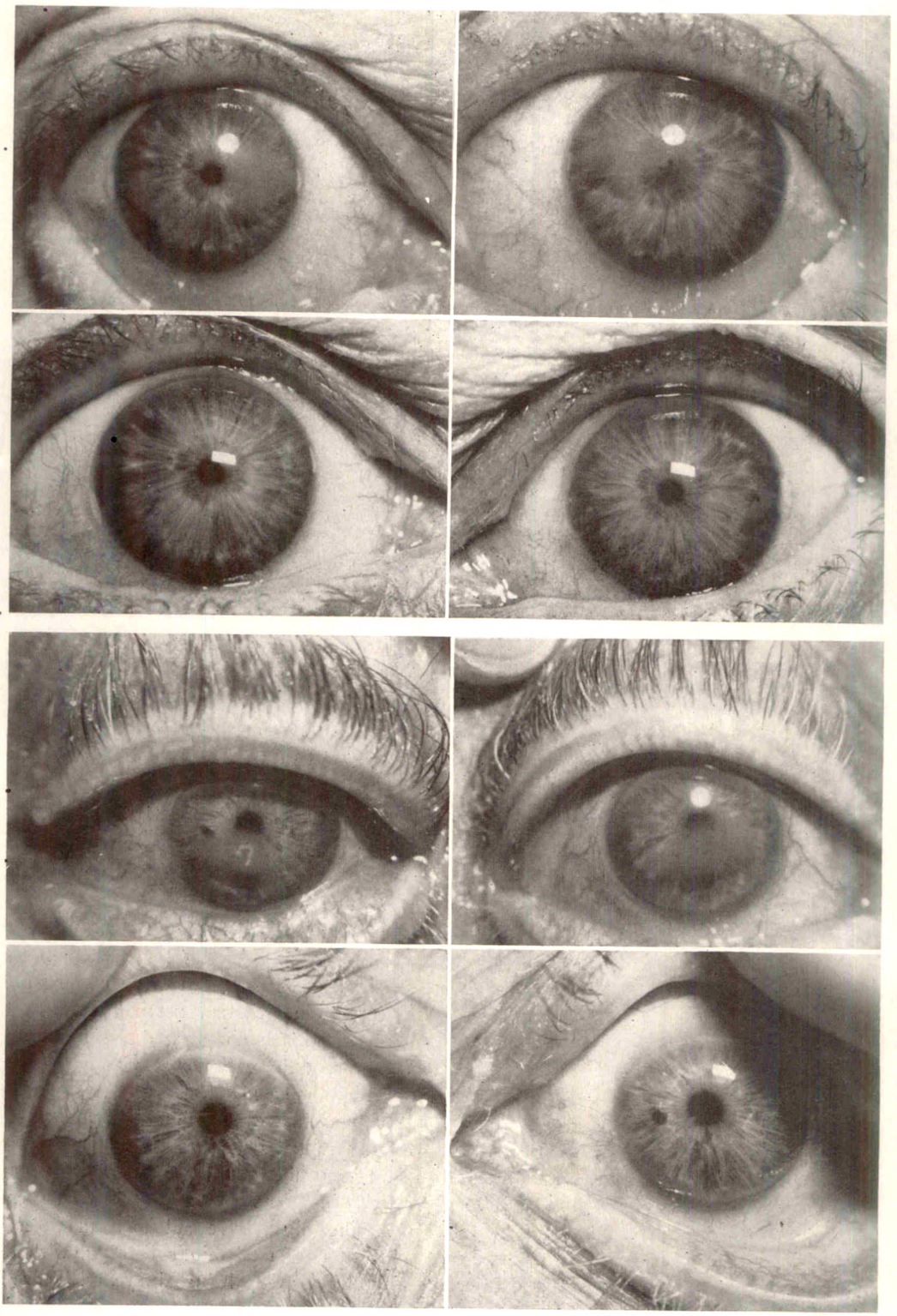

Fig. 2 (Kennedy, Roca, and Landers). Diagrammatic distribution of corneal changes in 18 patients observed over eight-year period; 15 had bilateral miotic treatment with bilateral involvement in 14. In three, the keratopathy occurred only in the eye under treatment.

mologists, these 18 cases represent the total to have become manifest over the past eight years.

These patients have been evaluated medically and by laboratory studies to rule out any ocular process such as irridocyclitis, phthysis bulbi, absolute glaucoma, or any systemic-related cause for a band keratopathy (such as parathyroid adenoma, dysproteinemia, vitamin D intoxication, sarcoidosis, chronic renal insufficiency).[1-3] Laboratory studies included calcium and inorganic phosphorous in all 18 patients. Thirteen had additional studies, including alkaline phosphatase, cholesterol, glucose, urea nitrogen, uric acid, total protein, albumin and other tests. All tests were negative in all 18 patients.

The only common denominator in this group of well-controlled glaucoma patients appears to be the long-term miotic therapy. This seems to be more than coincidence; particularly so, since we have not observed this atypical band keratopathy in non-glaucomatous patients in the absence of systemic or local causes. If this disorder is iatrogenic, it leads to speculation regarding the possible role of the miotic agents or their vehicles as the etiologic factor, or factors, in the production of these changes. Whether an altered metabolism of the cornea can be attributed to the medication, resulting in focal deposition consistent with the appearance of calcium, is an intriguing consideration. The pattern of

Fig. 4 (Kennedy, Roca, and Landers). Patient 2. Top: Bilateral keratopathy. Bottom: Clear corneas bilaterally after EDTA treatment.



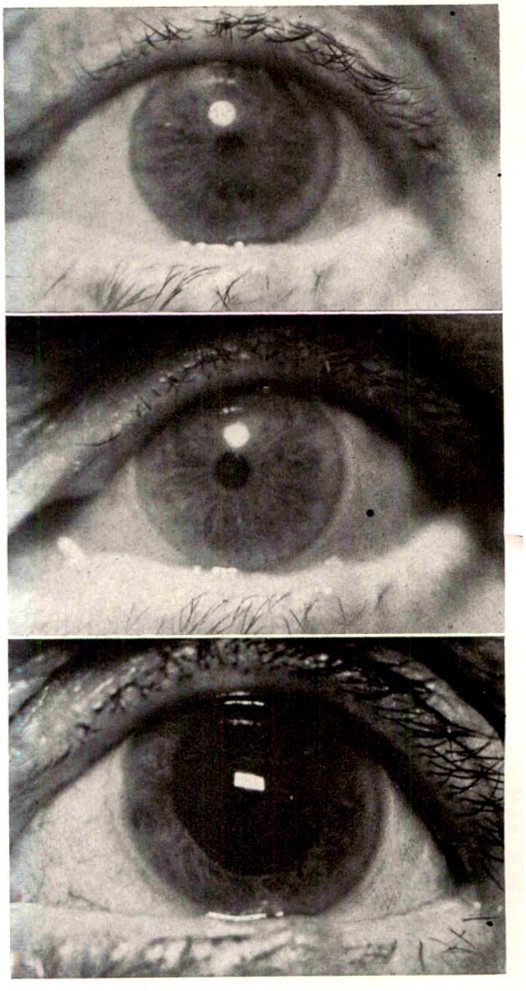


Fig. 5 (Kennedy, Roca and Landers). Patient 3. Top: Left eye with keratopathy (right eye was untreated and not involved). Center: Left eye with clear cornea after EDTA treatment. Bottom: Cornea in left eye remains clear after cataract extraction four years later.

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the keratopathy should be recognized clinically so as to spare the patient the unnecessary effort and expense of detailed medical and laboratory investigation for other causes.

To date animal experimental work with various miotics and drugs used in the vehicles has not reproduced the lesion.

In 1966, Charney[4] reported a case described as idiopathic band keratopathy, treated by lamellar keratectomy and studied pathologically. There were no ocular or systemic findings, but his 62-year-old patient had been treated for eight years with miotics for glaucoma. The tissue specimen revealed calcium and iron in the deeper epithelium and Bowman's area. This case appears to be identical to those presented in this report. While this case seems to supply a pathologic evaluation of this atypical band keratopathy, lamellar keratectomy is not to be considered the method of choice for treatment. Treatment should be medical rather than surgical. Chelation was recommended by Grant,[5] and later, Breinin and DeVoe[6] pointed out that chelation "should be the primary treatment in cases of band keratopathy and may make future corneal surgery unnecessary." Chelation can be carried out as an office procedure. Prognosis is excellent.

Commercial ophthalmic preparations for chelation as such are not available. The disodium salt of a synthetic chemical, ethylenediamine tetra-acetic acid (EDTA), used in scleroderma, vascular, and other medical problems, is available in ampoules of 150 mg /ml, and it can be converted very simply to an ophthalmic solution[7] by withdrawing 5 ml of the stock solution by syringe and injecting it into 120 ml of a standard buffered ophthalmic irrigating solution. This prepares an 0.02 molar solution. Following topical anesthesia and denuding of the epithelium, this can be applied to the involved corneal area by continuous drip or constant stream for 15 minutes. This is simple and the results are dramatic, with good recovery of vision. Of our 18 patients, 11 have been so treated since 1965, with improved vision and relief of irritative symptoms. Three patients with incomplete removal have continued to deposit more opacity in the nontreated portion of the cornea. The others have had no recurrences in spite of continued miotic therapy, with the longest follow-up being six years. There is

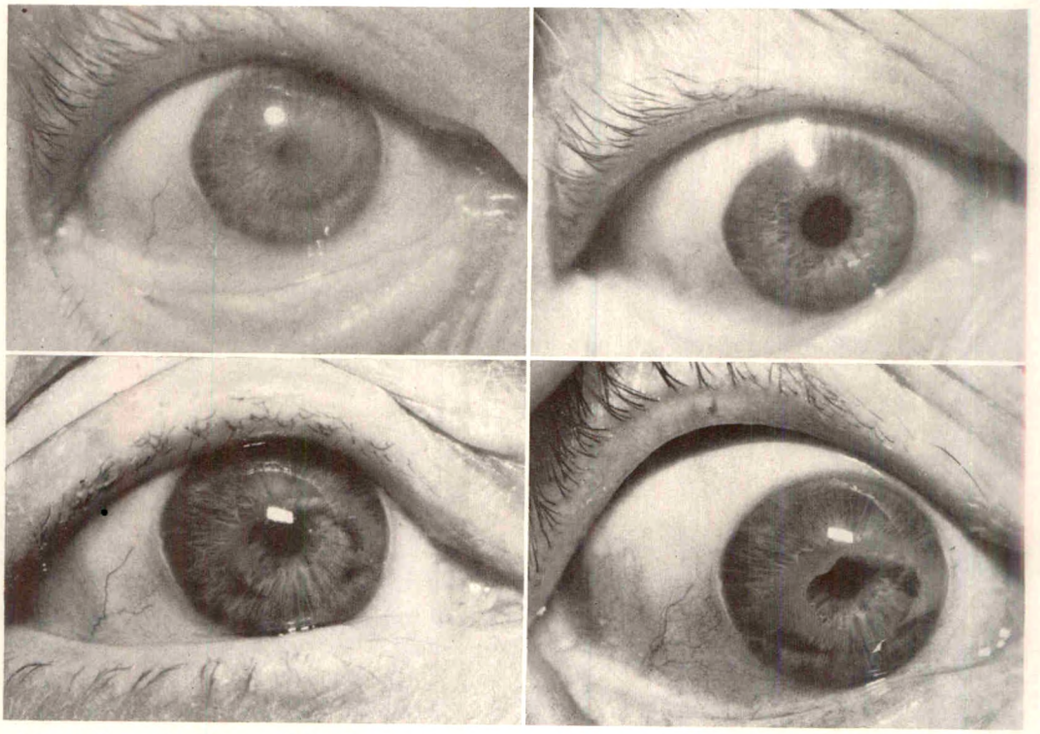


Fig. 6 (Kennedy, Roca, and Landers). Patient 4. Right eye. Top left: Vision 20/80 with keratopathy. Top right: Cornea clear, vision 20/20— one week after EDTA treatment. Bottom left: Further deposition in untreated area around area originally treated three years earlier. Bottom right: Two years later, further deposition, vision 20/25.

no reason why treatment could not be repeated.

Figures 3 through 7 show patients with the atypical band keratopathy before and after such treatment.

## Summary

An atypical band keratopathy was observed in 18 patients with well-controlled primary glaucoma, all of whom were receiving long-term miotic therapy. It is characterized by fine, gray granular deposition in the paracentral interpalpebral area of the

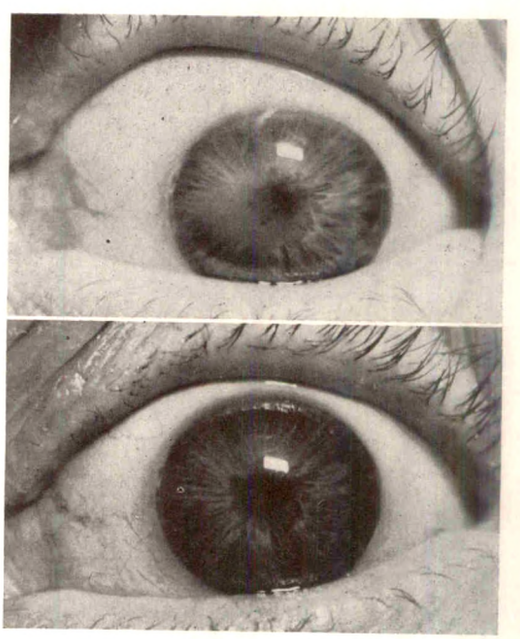


Fig. 7 (Kennedy, Roca, and Landers). Patient 4. Top: Left eye with keratopathy. Vision 20/30—. Bottom: Same eye with clear cornea after EDTA treatment. Vision 20/20.

cornea at the level of deep epithelium and Bowman's membrane and extends horizontally with progression.

The prognosis is excellent and satisfactory treatment by chelation with EDTA has proven the treatment of choice. Under topical anesthesia, this consists of irrigation with an 0.02 molar solution by continuous drip or constant stream for 15 minutes to the involved area of the cornea which has been denuded of epithelium. Eleven of 18 patients have been treated with improved vision and relief of irritation.

If this keratopathy is recognized, the patient can be spared detailed medical and laboratory investigation for other causes.

Etiologic factors have been considered, emphasizing the apparent role of the miotic agent, or more particularly their vehicles, in its production.

ACKNOWLEDGMENT

We thank Drs. John R. Fitzgerald, John F. Gipner, Harold J. Louis, and George A. Platt for allowing us to include their patients in this series.

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OPHTHALMIC MINIATURE




The eye of Horus.

# EFFECT OF OCULAR PIGMENTATION ON HYPOTENSIVE RESPONSE TO PILOCARPINE

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Ophthalmologists are aware that blue irides dilate much more promptly than do heavily pigmented, brown irides.[1-4] It is also generally accepted that cycloplegic agents are required in both greater quantity and concentration to obtain an adequate degree of cycloplegia in the latter category of patients.[5-7] One explanation for this is that the drug must penetrate through more dense pigment to reach receptor sites in darker eyes.[5-7]

The effect of ocular pigmentation on response to miotics, however, has not been well studied. If the hypothesis concerning mydriatics in pigmented eyes is correct, penetration of miotics to receptor sites should be impeded as well, and not only the pupillary, but also the hypotensive effects of these agents may be reduced. The present study was undertaken to see whether ocular pigmentation results in differences in the effects of miotics on intraocular pressure and outflow facility.

## METHODS

The study group was composed of 24 patients with open angle glaucoma, diagnosed by the criteria of elevated intraocular pressure, characteristic visual field loss, and cupping of the optic nerve heads. Patients were divided into three groups on the basis of ocular and systemic pigmentation. These were: a blue-eyed Caucasian group, a brown-eyed Caucasian group, and a group of Negro patients with heavily pigmented brown irides.

After obtaining initial baseline applanation intraocular pressures, tonography was performed with the Crescent unit and the outflow facilities calculated according to the Friedenwald tables. Patients were then given 1% pilocarpine to be used four times daily in the right eye only, with the unmedicated left eye serving as a control. At the conclusion of two weeks, applanation tonometry and tonography were repeated and the patients were started on 4% pilocarpine. During the final two-week period, 8% pilocarpine was utilized.

Statistical analysis for right eye/left eye differences within a group were done by mean pair differences, and those between groups were done according to the formula for grouped data. Student's t-test was used and p values of 0.05 or less were considered statistically significant.

## RESULTS

The initial right and left eye applanation intraocular pressures and outflow facilities for each group are given in Table 1. No statistically significant difference was noted.

Blue-eyed patients appeared to have a marked hypotensive response with 1% pilocarpine over that seen in the other two groups. A further, statistically significant decline in pressure was only reached in the latter patients with the 8% drug solution (Table 2). An adequate therapeutic effect was not really attained in the brown-eyed Caucasian patients until 4% drug concentration was employed, whereas 8% was necessary to elicit a comparable response in the black patients (Tables 1 and 2).

Initial improvements in outflow facility (C value) were seen with 1% drug concentration in all groups. Despite additional declines in intraocular pressure, no further statistically significant change in C value was noted (Table 1).

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TABLE 1

MEAN APPLANATION INTRAOCULAR PRESSURES AND OUTFLOW FACILITIES
(±standard error of the mean)

| Group | | Baseline | | 1% Solution | | 4% Solution | | 8% Solution | |
|---|---|---|---|---|---|---|---|---|---|
| | | R | L | R | L | R | L | R | L |
| Blue* (N=8) | IOP | 29.28 ±2.23 | 29.28 ±1.84 | 21.63 ±1.25 | 30.63 ±2.48 | 19.00 ±0.91 | 29.37 ±2.98 | 18.80 ±1.41 | 29.48 ±2.73 |
| | % | | | 30.00 | | 34.80 | | 36.00 | |
| | C | 0.08 ±0.01 | 0.08 ±0.01 | 0.11 ±0.01 | 0.08 ±0.01 | 0.12 ±0.02 | 0.09 ±0.01 | 0.12 ±0.02 | 0.09 ±0.01 |
| Brown* (N=7) | IOP | 28.55 ±1.93 | 29.05 ±2.15 | 24.58 ±2.24 | 29.00 ±2.52 | 20.10 ±2.10 | 27.28 ±2.78 | 20.14 ±2.43 | 28.00 ±2.46 |
| | % | | | 15.30 | | 26.10 | | 28.01 | |
| | C | 0.08 ±0.01 | 0.08 ±0.01 | 0.17 ±0.04 | 0.08 ±0.02 | 0.14 ±0.02 | 0.09 ±0.02 | 0.17 ±0.03 | 0.07 ±0.01 |
| Black* (N=9) | IOP | 28.15 ±2.03 | 28.29 ±1.94 | 24.22 ±1.41 | 28.10 ±1.30 | 22.10 ±1.60 | 27.11 ±1.27 | 21.11 ±1.61 | 27.10 ±1.38 |
| | % | | | 13.83 | | 18.49 | | 22.20 | |
| | C | 0.07 ±0.01 | 0.07 ±0.01 | 0.12 ±0.01 | 0.07 ±0.01 | 0.11 ±0.01 | 0.07 ±0.01 | 0.11 ±0.01 | 0.07 ±0.01 |

* Blue = blue-eyed Caucasian patients, Brown = brown-eyed Caucasian patients and Black = Negro patients.

No attempt was made to determine the degree of miosis in each group. Clinically, however, all patients had miotic pupils at the time of revisits during drug application.

## DISCUSSION

The data from the present study discloses that the ocular hypotensive response to pilocarpine is influenced by ocular pigmentation.

TABLE 2

P VALUES FOR STUDENT'S T-TEST FOR SIGNIFICANCE OF DIFFERENCE BETWEEN PILOCARPINE CONCENTRATION IN THE VARIOUS PATIENT GROUPS

| Solution Strength | Blue* | Brown* | Black* |
|---|---|---|---|
| Untreated and 1% | P<0.01 | P<0.05 | P<0.05 |
| 1% and 4% | P>0.05 | P<0.05 | P>0.05 |
| 1% and 8% | P<0.05 | P<0.01 | P<0.05 |
| 4% and 8% | P>0.05 | P>0.05 | P>0.05 |

* Blue = blue-eyed Caucasians, Brown = brown-eyed Caucasians, Black = Negro patients.

Blue eyes, which have the least amount of ocular pigmentation, had the greatest ocular hypotensive response to pilocarpine. In these eyes, the response to 1% drug solution was pronounced and, although additional declines in intraocular pressure were seen at 4% and 8%, these were not of great magnitude. By contrast, brown eyes of Caucasian patients had statistically significant changes in intraocular pressure with the 1% solution, but required an increase in dosage to 4% to produce therapeutically meaningful responses. Responses to pilocarpine in the black patients were not as good as either of the two preceding groups at any drug concentration. The resulting shift in the dose-response curve was such that, in these eyes, an 8% solution produced a response roughly equal to that seen with 4% in brown eyes. The correlation of outflow facility changes and ocular pigmentation paralleled those noted with intraocular pressures.

Statistically significant changes in intraocular pressure were noted during the course of the study without meaningful alterations in outflow facility. This lack of correlation between ocular hypotensive response and change in outflow facility was previously noted with pilocarpine, indicating that this drug may affect aqueous production as well as response to aqueous outflow.[8,9] Experimental data in several species confirmed this finding.[10,11] Furthermore, it has been shown that the dose-response curves for pilocarpine alone and for pilocarpine plus epinephrine are parallel, again implicating a duel mechanism of action for pilocarpine.[12]

One hypothesis to explain the observations of this study is that ocular pigment might bind topically administered drugs which would then fail to reach receptor sites in the iris and ciliary body. It is also possible that enzymatic differences exist coincidentally in pigmented ocular structures. Increased activity of iris dopa-oxydase has been postulated to explain the difference in response of albino and pigmented rabbit irides to adrenergic drugs.[13] This idea, however, appears a less likely explanation, since the degree of pigmentation influences the responsiveness to a wide variety of drugs (e.g., cycloplegics, mydriatics, and pilocarpine), thereby necessitating a vast number of enzymatic differences being called into play.[1-4]

From the present data, it would seem that the change in the dose-response curve should be borne in mind when using pilocarpine, particularly in black patients. In this instance, recourse to pilocarpine solutions in excess of 4% may be required. Also, studies with this drug should specify the distribution of ocular pigmentation in either patients or experimental animals in order to make interpretation of data more meaningful.

## Summary

Pilocarpine was administered in three strengths (1, 4, and 8%) to three groups of patients with open-angle glaucoma patients: Caucasians with blue irides, Caucasians with brown irides, and black patients with heavily pigmented, brown irides. It was found that blue eyes demonstrated near maximal ocular hypotensive responses with 1% pilocarpine. Black patients demonstrated a relative resistance to the ocular hypotensive response of this drug until the higher concentrations were reached. Brown-eyed Caucasian patients were intermediate in response between these two extremes. The results are consistent with the idea that ocular pigmentation hinders penetration of topically applied drugs to receptor sites. This shift in the dose-response curve should be considered when treating glaucomatous black patients.

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# INTRAOCULAR PRESSURE CHANGES DURING HEMODIALYSIS

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Increased intraocular pressure (IOP) has been observed during hemodialysis in uremic dogs and in uremic patients.[1-6] It also has been suggested that since tonometry is effective in detecting IOP changes due to fluid transfer across the blood-aqueous barrier during dialysis, increases in IOP may parallel and thus predict fluid movement across the blood barrier as in the development of cerebral edema during dialysis.[1,3]

This study was undertaken to further evaluate changes in IOP with hemodialysis and to determine whether a correlation exists between hourly changes in serum osmolality and IOP.

## METHODS

Twenty patients receiving chronic intermittent hemodialysis were studied. All dyalyses were performed using the Kolff twin-coil unit with Ultra-flo 145 (Travenol Laboratories, Inc.) coils. The purpose of dialysis was to remove excess fluid weight as well as excess chemical constituents, such as urea nitrogen and creatinine. Intraocular pressures were measured with a Tonair applanation tonometer. This instrument was demonstrated to give comparable readings to the Goldmann applanation tonometer on 50 consecutive patients in the University of Colorado eye clinic. Measurements were made, with the patient in supine position, on both eyes of each patient before dialysis, every hour during dialysis and at the conclusion of dialysis. Since the readings for both eyes were similar in almost every instance the mean value of the two eyes was determined for data analysis. When IOP readings were 25 mm Hg or more, a series of readings were taken and the recorded values were based upon the higher readings as recommended by Posner and Inglima in their evaluation of the Tonair Applanometer.[7]

The duration of the dialysis was six hours in nine patients and five hours in 10 patients. In one patient, the dialysis had to be terminated at three hours following a convulsion; this patient was dropped from the study.

Arterial blood samples were collected for determination of serum osmolality (freezing point depression method, using an Advanced Osmometer) each time tonometry was performed. Specimens were allowed to clot, were centrifuged, and the individual serum samples stored at 4°C until osmolality determinations were performed.

After collection and analysis of the IOP and serum osmolality data it was suggested that tonographic data may be of use in the interpretation of the findings. Unfortunately, when the tonographic study was undertaken only three of the original group of subjects were available for study; the others were deceased, had moved from the area or were transplant recipients. Therefore, four additional subjects were admitted to the tonographic study. Tonographic recordings (and Tonair measurements) were made just before dialysis and at the four-hour stage during dialysis. The mean value of tonographic data from the two eyes was used for analysis.

## RESULTS

All patients in this study exhibited a decrease in body weight at the conclusion of dialysis.

The mean initial serum osmolality was 311

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TABLE 1

INITIAL AND FINAL VALUES OF IOP AND SERUM OSMOLALITY

| | Five-Hour Group (10 patients) | Six-Hour Group (9 patients) | Combined Groups |
|---|---|---|---|
| Osmolality (mOsm/L): | | | |
| Initial | 311 (291, 331)* | 313 (299, 331)* | 312 (291, 331)* |
| Final | 282 (267, 303) | 282 (273, 290) | 282 (267, 331) |
| Mean change | −29.5 (−24, −43) | −31.1 (−12, −42) | −31 (−12, −43) |
| IOP (mm Hg): | | | |
| Initial | 20.4 (15.5, 32.5) | 20.6 (15, 28) | 20.5 (15, 32.5) |
| Final | 18.9 (12, 31) | 22.7 (16, 32.5) | 20.7 (15, 32.5) |
| Mean change | −1.45 (−5, +8) | +2.06 (−5, +9.5) | −0.2 (−5, +9.5) |

* The numbers in parentheses refer to the range of values.

mOsm/L (range 291-331) and 313 mOsm/L (299-331) in the patients dialyzed five and six hours, respectively. The mean starting osmolality for all 19 patients was 312 mOsm/L. Serum osmolality decreased during dialysis in every patient. The change between initial and final osmolality in the five-hour group was −29.5 mOsm/L (12-42) and that in the six-hour group was −31.1 mOsm/L (12-42). These figures are presented in Table 1.

The predialysis IOP of all 19 patients ranged from 15-32.5 mm Hg with a mean of 20.4. The mean initial IOP and range for the five- and six-hour group was 20.4 (15.5-32.5) and 20.6 (15-28) respectively. The five-hour group exhibited a mean change in IOP of −1.45 with a range of −5 to +8. That in the six-hour group was +2.05 with a range of −5 to +9.5. Combining the five- and six-hour groups we find only a 0.2 mm Hg increase in IOP at the conclusion of dialysis (Table 1).

Despite the lack of significance between initial and final IOP, careful analysis of IOP changes during dialysis revealed some interesting points. The changes are presented in Table 2 and Figure 1. For convenience all 19 patients are grouped together for IOP and osmolality values between zero

TABLE 2

MEAN IOP AND SERUM OSMOLALITY AT HOURLY INTERVALS DURING DIALYSIS*

| | Initial | One-Hour | Two-Hour | Three-Hour | Four-Hour | Five-Hour | Six-Hour |
|---|---|---|---|---|---|---|---|
| IOP (mm Hg) | 20.5 ±1.0 | 20.1 ±1.4 | 19.2 ±1.1 | 21.1 ±1.3 | 21.1 ±1.2 | 21.3 ±1.4 | 22.7 ±1.8 |
| Osmolality (mOsm/L) | 313 ±2.5 | 305 ±2.4 | 299 ±2.3 | 294 ±2.2 | 289 ±2.1 | 284 ±2.0 | 282 ±2.0 |

* Values are arithmetic mean, ± standard error of the mean. Up to and including five hours, each group contains 19 patients. The six-hour group has only nine patients.

and five hours. It can be seen that a significant decrease in IOP occurred during the first two hours (from 20.4 to 19.0 mm Hg, $p<.05$). The increase in IOP between two and three hours (19.0 to 20.9 mm Hg) was significant at the 99% level. However, the IOP from three to six hours was not significantly different from the baseline value. The apparent marked increase at six hours is due to the smaller number of observations since only nine patients were dialyzed a full six hours. These IOP changes are not, however, considered clinically significant.

When the IOP changes in individual subjects are considered, marked alterations are evident. In 10 of the 19 patients there was a maximum rise in IOP ranging from 0.5 to 16 mm Hg, with a mean of 6.9 mm Hg. This increase occurred from one to six hours after dialysis was started. The remaining nine patients exhibited either no significant change or a sustained reduction in IOP during dialysis. When the mean IOP changes of the entire group are considered only with respect to time, individual elevated pressures are masked.

The mean value of outflow facility obtained by tonography before dialysis was 0.22 ± .026 (S.E.) and that after four hours was 0.21 ± .027. The IOP values for this smaller group of subjects exhibited a similar maintained elevation at four hours as was ob-

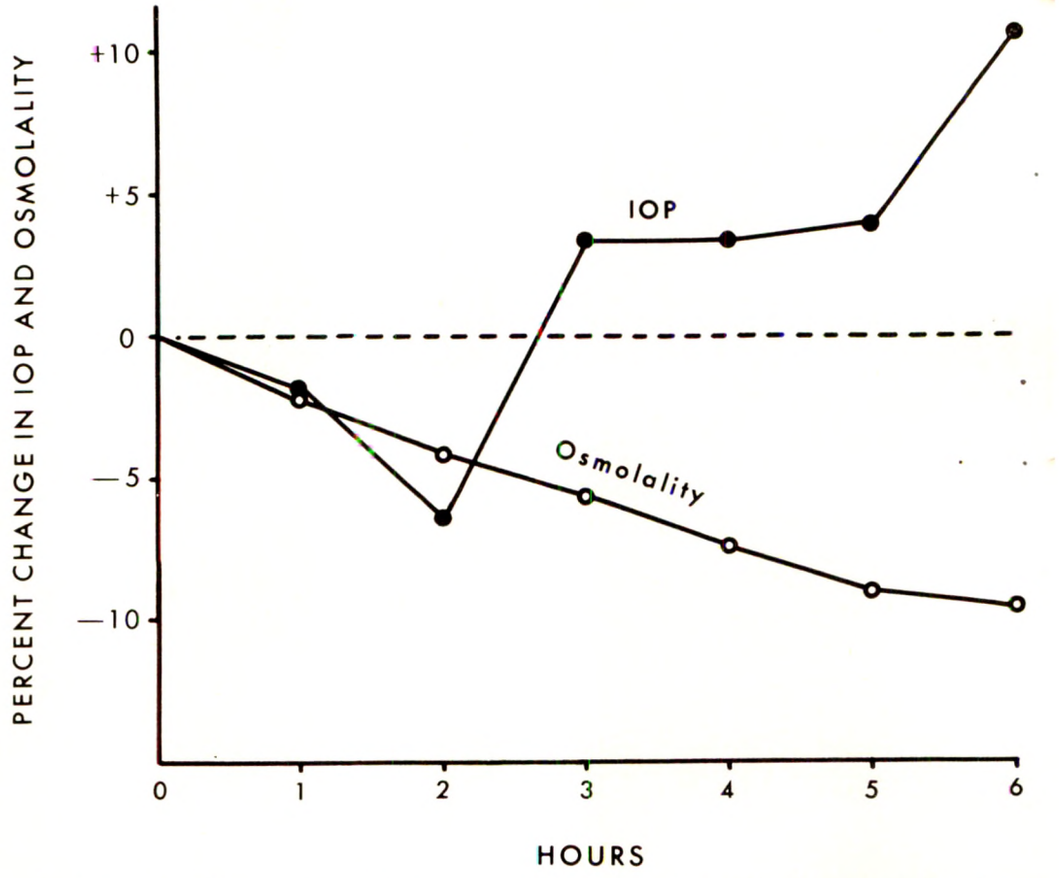



Fig. 1 (Ramsell, Ellis, and Paterson). Changes in IOP and serum osmolality with respect to time during dialysis. Percent change was calculated from the figures in Table 2. It should be noted that the six-hour points are the mean values from only nine patients; the other points are obtained from 19 patients (see text).

served in the original 19 subjects; the mean IOP before dialysis was 20.5 ± 1.03 and 24.6 ± 1.60 after four hours of dialysis.

The patients exhibiting abnormally high IOP readings in this study were found to have normal applanation tensions, visual fields, and gonioscopic findings when examined in the eye clinic on a day when they were not undergoing dialysis.

## Discussion

In the study reported by Sitprija, Holmes and Ellis[1] from this Medical Center in 1964, there was a mean decrease in serum osmolality of 37.6 mOsm/L (range 3-72) after about six hours dialysis. This compares with a mean fall in serum osmolality of 31 mOsm /L (12-43; 5 and 6 hour groups combined), in the present study. Despite the use of smaller coils in this study, 1.45 $m^2$ (Ultra-flo 145) as opposed to 1.9 $m^2$ (Twin-coil 190, Travenol) used in the earlier study,[1] the observed changes in osmolality are obviously not significantly different.

Sitprija and associates[2] found an average increase in IOP of 41.8% of control values in uremic dogs following dialysis, and an average increase in IOP of 4 to 8 mm Hg in the majority of uremic patients during dialysis. Watson and Greenwood[3] reported an average rise in IOP of 8.1 mm Hg in six patients during 12 dialyses. Biagini and Gloria[4] reported a mean increase in IOP of 16% during dialysis of uremic patients. Applemans and associates[5] demonstrated an increase in IOP up to 10 mm Hg in 80% of patients undergoing renal dialysis. These studies suggest a correlation between decrease in plasma osmolality and increase in IOP during dialysis. Presumably an influx of fluid into the eye due to the difference in osmolality between plasma and intraocular fluids results in an increased IOP. In none of the previous studies however was data presented which correlated hourly serum osmolality changes with increases in IOP. The data obtained in this study not only confirm that individual increases in IOP can occur during dialysis but can also be analysed to compare hourly changes in IOP and serum osmolality.

In Figure 1 the hourly percent of change in serum osmolality is plotted against the hourly percent of change in IOP. As described in Results, an initial decrease in IOP is followed by an increase which persists up to six hours. The initial decrease in IOP might be related to decreased intravascular volume as well as to reduced anxiety in the patients as the procedure became more familiar. The initial weight loss in patients undergoing dialysis represents principally a reduction in intravascular volume.[8] Marked decreases in IOP paralleling weight loss in dogs were observed by Sitprija and associates.[2] The increase in IOP between two and three hours is felt to be due to an osmotic influx of water into the eye as a result of the relative hyperosmolality of intraocular fluids. During ensuing hours it is presumed that the intraocular and intravascular fluids approach osmotic equilibrium.

It had been suggested to us that the maintained elevation of IOP at three to four hours might be due to a decrease in outflow facility. For this reason tonographic measurements were made before and after four hours of dialysis. The results, which demonstrated no change in outflow facility, indicate that it is not a significant factor in explaining IOP changes observed during hemodialysis.

Changes in IOP during hemodialysis might be related to the hourly rate of serum osmolality change; a more rapid decrease in serum osmolality resulting in a more pronounced IOP change. IOP in uremic dogs during hemodialysis remained unchanged or showed a minimal increase when the reduction in serum osmolality averaged 8.5 mOsm /L per hour. When the serum osmolality reduction averaged 11 mOsm/L per hour the IOP increased significantly.[2] In the present study serum osmolality decreased at 5-7 mOsm/L per hour and mean IOP changes were not significant.

Barry, Khoury, and Brooks[9] found that, although changes in mean serum osmolality appear to be associated with reciprocal changes in IOP, the two are not closely related. Galin, Aizawa, and McLean[10] consider that the water-drinking test, at its outset, depends upon the level of induced hypo-osmolality, but add that in man the statistical correlation between plasma hypo-osmolality and IOP increase is not adequate to make this an inviolate hypothesis.

It should be recalled that in the present study marked increases in IOP during hemodialysis did occur at various times in 10 of the 19 patients, but the times did not correlate with any particular stage of serum osmolality reduction. The possibility exists that the degree and timing of IOP increases during hemodialysis depends principally upon the extent of changes in intravascular volume. In those patients exhibiting the greatest IOP increase during dialysis the initial fall in IOP (Fig. 1), which is considered to correlate with weight changes, was minimal.

It can be concluded that during hemodialysis IOP is affected by factors other than a relative reduction in serum osmolality. Krupin, Podos, and Becker[11] have suggested that the ocular hypotensive response to hyperosmotic agents might be mediated, in part, by mechanisms in the central nervous system.

## Summary

In 19 uremic patients undergoing hemodialysis the mean final IOP was only 0.2 mm Hg above the mean initial values. However, in 10 of the 19 patients maximum increases in IOP ranging from 0.5 to 16 mm Hg occurred at times ranging from one to six hours. Statistically, but not clinically significant mean IOP changes were observed during the early stages of dialysis and are discussed. Serum osmolality decreased in all patients; the mean decrease was 31 mOsm/L. Hourly IOP changes did not correlate with reduction in serum osmolality. The influence of changes in intravascular volume on IOP during hemodialysis is discussed.

### Acknowledgment

We acknowledge the cooperation of members of the Renal Division during this study.

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# A TECHNIQUE FOR CONJUNCTIVO-DACRYOCYSTORHINOSTOMY

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In the performance of conjunctival and dacryocystorhinostomy procedures, anatomical variations of the distance from the caruncle to the center of the nasal cavity, the size and shape of the nasal cavity, the position of the septum, and the different possibilities of the angle of the channel require that each patient be custom-fitted with a Jones tube of optimum length. Accordingly, I have devised a set of 20 tubes, varying by 1 mm from 10 to 30 mm, (Fig. 1). Each tube has an outside diameter of 3 mm, a lumen of 1.70 mm and a flange of 4 or 5 mm.

Observation of the mechanical difficulties that beset the ophthalmic surgeons at the Eye Foundation Hospital led to the development of a set of instruments (Fig. 2) designed to make the operation technically easier with less trauma to the patient and successful function of the tube more likely.

From the Department of Photography, the Eye Foundation Hospital, Birmingham, Alabama.

Reprint requests to Mr. Clarence William Cox, Jr., Photographer, The Eye Foundation Hospital, 1720 Eighth Avenue South, Birmingham, Alabama 35233.

## PROCEDURE

At our hospital, the operation for emplacing a Jones tube is begun by incising the skin and subcutaneous tissues over the lacrymal area as for a dacryocystorhinostomy. After the tissues are retracted, a sector of lacrymal bone is removed with a burr, a chisel, or an Iliff trephine on a Stryker saw. The nasal mucosa beneath the bone sector is removed also. The lower half of the caruncle is removed and from this conjunctival opening at the medial end of the fornix, a stab inci-

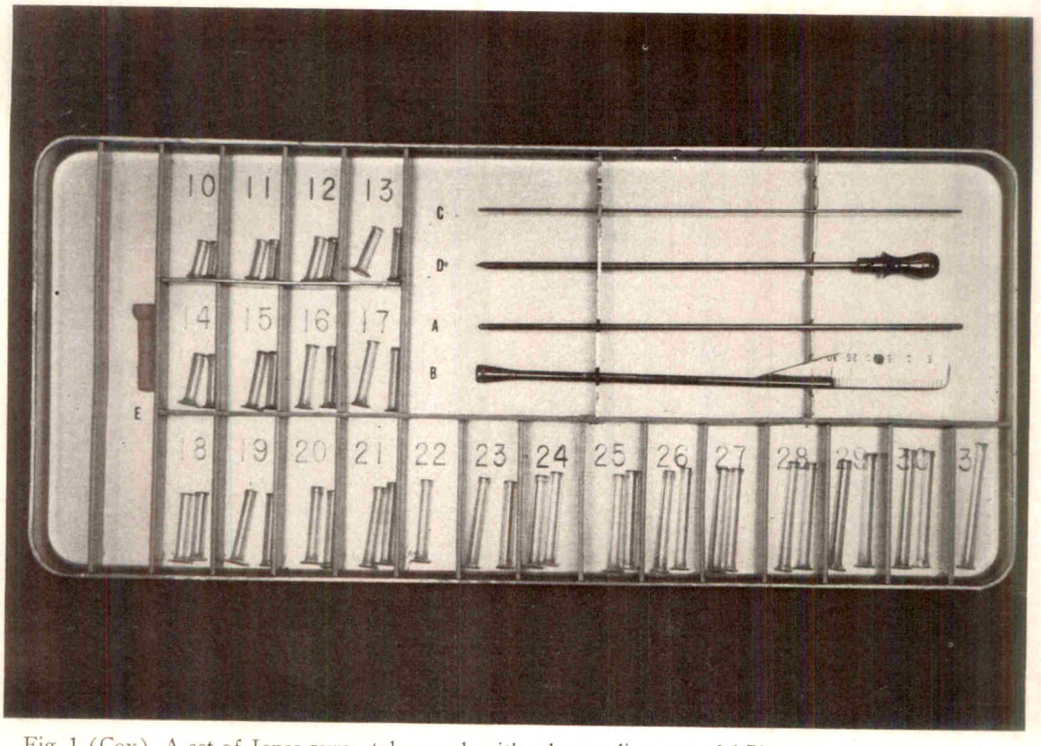



Fig. 1 (Cox). A set of Jones pyrex tubes, each with a lumen diameter of 1.70 mm, and varying by 1 mm from 10 to 30 mm, are kept in an aluminum compartment case. The case also contains special instruments for insertion of the proper tube.

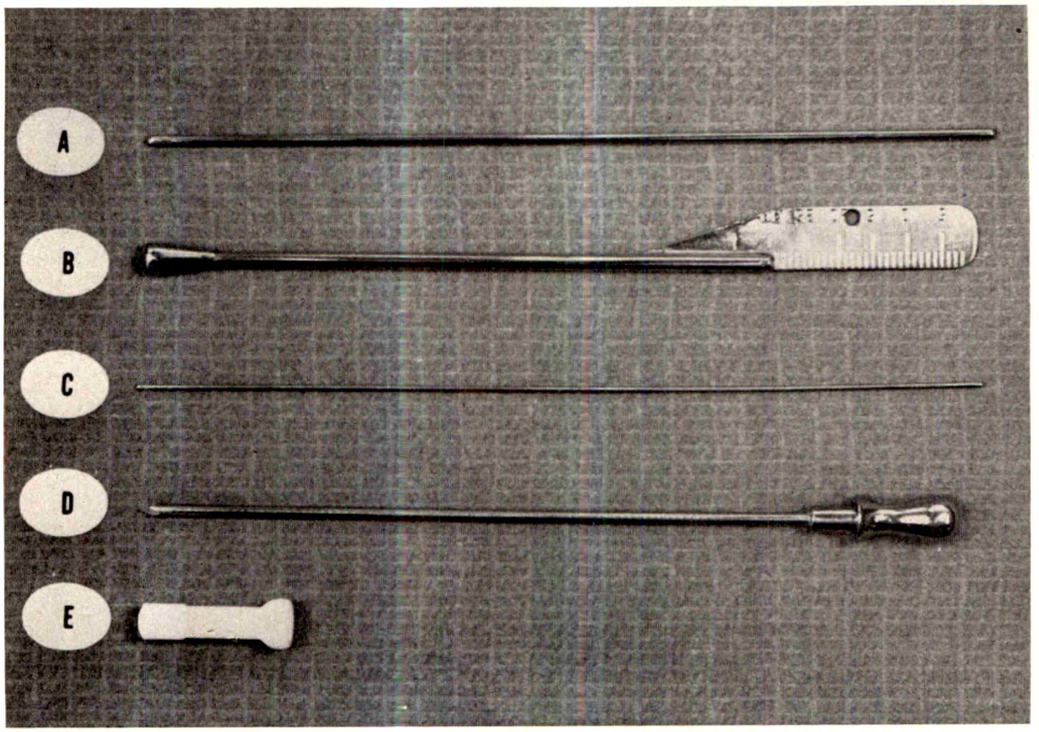



Fig. 2 (Cox). The special instruments for insertion of the tube of proper length are: (A) Stainless steel precision rod (1.6 mm in diameter and 12.5 cm long). (B) Precision millimeter gauge. (C) Stainless steel precision rod (0.75 mm in diameter). (D) Trocar. (E) Teflon inserter.

sion is made with the rounded Beaver blade knife into the bony opening. A stainless steel precision rod, 1.6 mm in diameter and 12.5 cm long, rounded on both ends, is inserted from the caruncular opening into the nasal cavity (Fig. 3-A). With the tip of the rod touching the septum, the sleeve with a millimeter gauge is slipped on the rod and pushed down to the caruncle. The proper length of the tube is indicated. A 3 mm clearance is allowed from the nasal septum (Fig. 3-B). The sleeve-gauge is then removed and a tube of optimal length is placed on the rod. The Teflon inserter, designed to exert even pressure around the top of the tube at the flange, is placed on the rod (Fig. 3-C) and is pushed so that the tube is placed into position (Fig. 3-D). Observation of the tube transnasally and through the surgical window will assure that the tube is the proper length and optimally positioned. Also, the upper end of the tube must not slip deeply into the fornix, or conjunctiva will grow over the top of the tube.

*Postoperative measures*—After the operative edema subsides, a different length tube may be required. In most cases, the tube may be changed as an office procedure without anesthesia, even in children. The rod is inserted through the tube. The tube is slid out, leaving the rod in place, and a longer or shorter tube, as indicated by the gauge, is inserted without trauma. A thinner rod, 0.75 mm in diameter (Fig. 2-C), is used if mucus or discharge has partially blocked the tube, making it difficult to insert the 1.6 mm rod.

If a patient loses a tube, and is not seen for several days by the surgeon, the channel is usually closed with scar tissue, especially if this occurs soon after insertion. The trocar in the set (Fig. 2-D) can be used to reopen the surgical channel and the emplacement with the steel rod is repeated. This may be done under local anesthesia in the office or

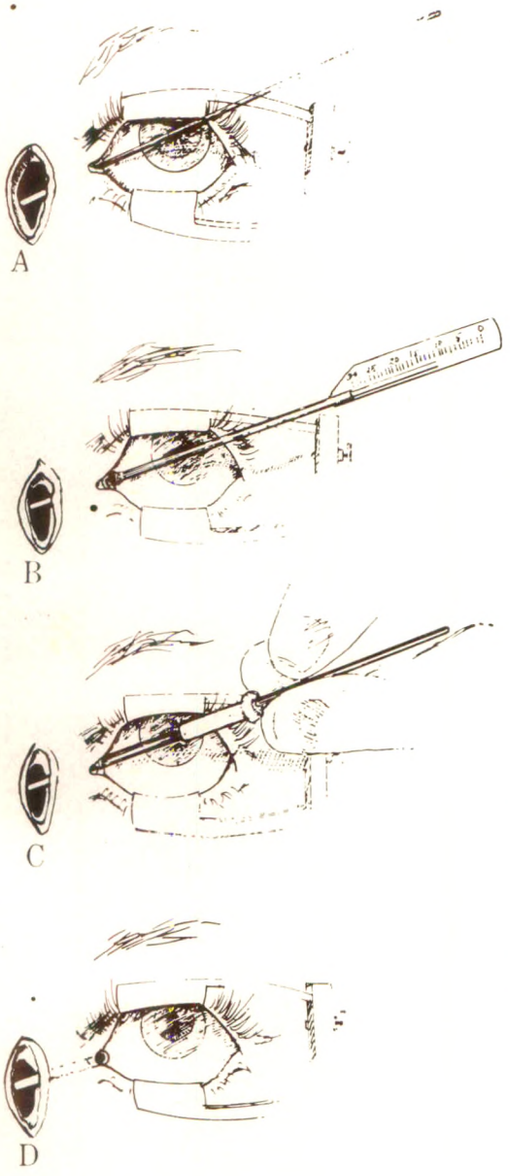



Fig. 3 (Cox). Technique used for emplacement of the Jones pyrex tube by the Cox system. (A) Shows the 1.6 mm precision rod placed in the channel made for the tube, extending from the caruncle through the soft tissues of the medial canthal area and extending through the bony opening into the nasal cavity. (B) The precision millimeter gauge is introduced to measure the length needed. (C) The tube of proper length is inserted with the Teflon inserter. (D) Jones pyrex glass tube now in place.

under general anesthesia in the hospital, depending upon the patient's age and ability to cooperate. The set of instruments and tubes is contained in an aluminum compartment case suitable for autoclaving, dry heat, or gas sterilization. Gas sterilization is recommended as it causes no water residue in the tubes.

## Summary

In order to facilitate conjuncival and dacryocystorhinostomy procedures, a sent of 20 pyrex glass tubes, varying by 1 mm from 10 to 30 mm was devised to span the tissues from the lower edge of the caruncle into the middle of the nasal cavity, according to the anatomical variations of different patients.

Enclosed with the set is a stainless steel rod which can be inserted through the surgical passageway for the tube, a precision millimeter gauge for determining the proper length of the tube, a precision rod 0.75 mm in diameter for use when the tube is blocked with blood or mucus, and a Teflon inserter.

## Acknowledgment

I thank Dr. Alston Callahan for encouraging my efforts in the development of this method.

# DERMATOPHYTOSIS AFFECTING THE PERIORBITAL REGION

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*San Francisco, California*

Most fungal infections of the cornea are secondary infections, caused by opportunistic fungi that have invaded a diseased cornea or one that has been treated with corticosteroids or broad-spectrum antibiotics. Two exceptions are corneal infections due to Candida albicans or Aspergillus species; these may infect an apparently normal cornea after minimal trauma.

Superficial mycotic infections can be divided into three groups: those caused by (1) the dermatophytes or ringworm fungi, (2) the organisms responsible for tinea versicolor and tinea nigra, and (3) Candida species.[1] It is better to restrict the term dermatophytosis to infections due to the ringworm fungi (the genera Microsporum, Trichophyton, and Epidermophyton) than to use it as an inclusive name for cutaneous fungal diseases.[2]

The dermatophytes occasionally infect the skin of the eyelids[3-11] or the eyelashes.[6-13] This paper reports a case of dermatophytosis of the eyelids due to the organism Trichophyton mentagrophytes.

## Case report

A four-year-old white boy had a pruritic rash around the right eye of four weeks' duration (Fig. 1). A "sty" of the right upper eyelid had opened and drained spontaneously one week before we saw him, and during that week, polysporin ointment was applied three times daily. Prior to the onset of symptoms, the child had played with an apparently normal pet rabbit. The child had a history of otitis media and allergy to certain foods.



Fig. 1 (Ostler, Okumoto, and Halde). Appearance of patient 30 days after onset of symptoms.

Examination revealed vesicles and pustules on an erythematous base that extended from the brow over the entire upper eyelid to the midline of the nose, thence to the lower eyelid and laterally several millimeters to the lateral canthus. There was minimal crusting. The conjuctiva and cornea appeared normal. Two moderate-sized, firm, nontender, anterior cervical nodes were palpable on the affected side. The lashes and hair of the eyebrows did not fluoresce under Wood's light.

The diagnostic possibilities appeared to be pyoderma or herpes simplex infection. Treatment of the eyelids was stopped, and two days later the lesions were elevated and more heavily crusted (Fig. 1). Several members of the staff of the Dermatology Division were consulted, and in their opinion the lesion resembled pyoderma.

The appearance of the lesions changed very little during the first two weeks of observation, in spite of the immediate institution of topical erythromycin ointment, hot packs, and 5% ammoniated mercury, and the addition of systemic erythromycin, 100 mg four times daily, at the end of the first week of treatment. At the end of the second week, all topical medication was stopped and the hot packs were changed to warm milk packs.

At this time, six weeks after the onset of symptoms, the skin lesions began to show improvement for the first time; both the erythema and the crusting diminished. Three weeks later (nine weeks after onset), moderate crusting of the eyelid margin

From the Francis I. Proctor Foundation for Research in Ophthalmology, the Department of Ophthalmology, and the Department of Microbiology, University of California, San Francisco. This study was supported in part by Public Health Service Research Grant EY-00310 (Drs. Ostler and Okumoto), and AI-00299 (Department of Microbiology).

Reprint requests to H. Bruce Ostler, M.D., Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco, Parnassus and Third Avenue, San Francisco, California 94122.

Dopamine-β-hydroxylase catalyzes the β-hydroxylation of dopamine to form norepinephrine.[21] It is of interest to note that in a separate study of catecholamine metabolite formation in the retina following dopamine infusion,[22] we found little formation of norepinephrine and almost no formation of normetanephrine, although other dopamine metabolites (DPA and HVA) were present. This is in contradistinction to the striking formation of norepinephrine from dopamine in the uveal tissues in the present study (Fig. 3). These findings are consistent with the fact that little or no norepinephrine is found endogenously in the mammalian retina and that dopamine is the only catecholamine which seems to be present in this tissue.[14,23] The inference is clear that dopamine-β-hydroxylase is active in the uveal tract, but is not present in retinal catecholamine-containing neurons.

## Summary

Following intracarotid infusion of tritiated catecholamines ($^3$H-norepinephrine or $^3$H-dopamine) in cats, radiochromatography of extracts of the iris and ciliary body was done. After norepinephrine infusion, small amounts of radioactivity were found associated with catecholamine metabolites, although most remained associated with the original norepinephrine. After dopamine infusion, on the other hand, a large amount of radioactivity became associated with norepinephrine, suggesting conversion of the infused dopamine to norepinephrine. This was consistent with the high concentration of endogenous norepinephrine found in the anterior uveal tract, and was in contradistinction to the retina, in which dopamine is the only catecholamine present in significant endogenous amounts.

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OPHTHALMIC MINIATURE

There was another woman who rushed in, drawing attention to a thing like a tiny bead of glass sticking to her baby's cheek. The child had acute inflammation of the eyeball, which the mother had treated with cold tea. The eye had long been closed, but when the mother made a clumsy attempt to open the swollen lid something had popped out, some fluid and this thing like glass. She was afraid to touch it. She viewed it with horror as a strange thing that had come out of the eye. Hugging the child, she had run a mile or so with the dread object still adhering to the skin of the cheek. This glistening thing was the crystalline lens. The globe had been burst, and the child was, of course, blind.

Sir Frederick Treves
*The Elephant Man*
London, Cassell, 1923

# NORRIE'S DISEASE

## Congenital Progressive Oculo-Acoustico-Cerebral Degeneration

Allan H. Fradkin, M.D.

*Galveston, Texas*

Norrie's Disease is a rare type of progressive, hereditary, congenital degeneration of the eye, ear, and brain. The entity was named for Gordon Norrie, consulting ophthalmologist to the Royal Danish Institute for the Blind, who described several cases of blindness under the name of atrophia oculi congenita.[1] Warburg published the first Danish pedigree and suggested the eponym for this syndrome; her extensive monograph[2] summarized the cases from all geographic areas of the world. At present there are only four known families with Norrie's disease in the United States.[3-6]

Although previously included in a familial survey by Holmes,[6] the patient present in this report warrants a separate report, since he is the youngest patient diagnosed with Norrie's disease and, therefore, affords us a view of the evolution of ocular changes, possibly permitting the earlier recognition of this entity, and thus allowing genetic counseling for the parents.

### Case report

This white boy was born at the University of Texas Medical Branch on November 10, 1969, after an unremarkable pregnancy, labor, and delivery. I was consulted when the child was 12 hours of age because of his anisocoria.

Ophthalmologic examination revealed decreased orbicularis function on the left, but was otherwise unremarkable externally. The globes were of normal size. Each eye showed a random gaze pattern independent of the other. Chemical conjunctivitis from silver nitrate instilled at birth was present.

Both corneas were clear and measured approximately 10 mm. The anterior chambers were shallow. The right pupil measured 2 mm and was sluggishly reactive to light; the left was 5 mm and nonreactive Rubeosis iridis was present bilaterally. The lenses were clear.

From the Department of Ophthalmology, University of Texas Medical Branch. This study was supported in part by Public Health Service Grant 5T01 EY 0058 05 from the National Institute of Health.

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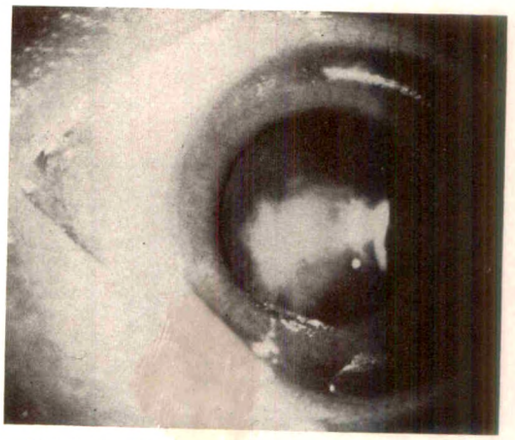


Fig. 1 (Fradkin). Left eye, showing vitreous hemorrhage (black in picture) and yellowish membrane (white in picture).

Fundus examination revealed no normal retinal tissue in either eye and was very difficult to interpret. Vitreous hemorrhages were seen bilaterally in addition to a yellowish-white vascular membrane (Figs. 1 and 2). Ocular tensions were normal by palpation.

Family history was then elicited (Fig. 3). The X-linked recessive inheritance pattern is apparent, since only males are affected and the trait can be passed on through carrier females who are themselves normal. It is of interest that the patient's family originated in Sweden, which is where the majority of cases have been found. Of the two maternal uncles affected with Norrie's disease, one had both blindness and retardation and the other had

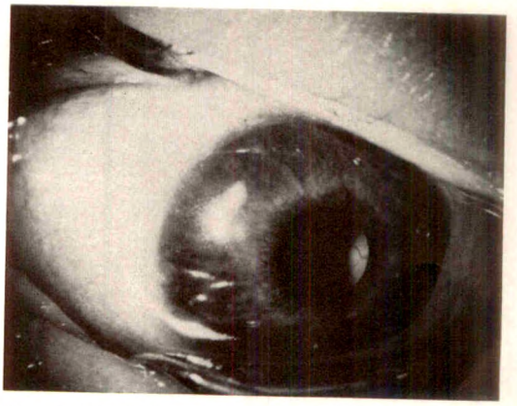


Fig. 2 (Fradkin). Right eye, showing retrolental vascular membrane.

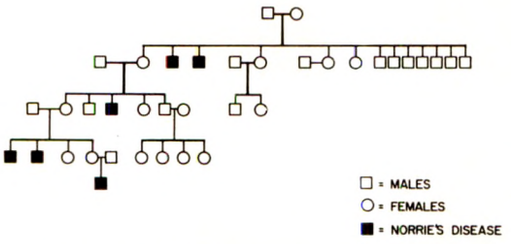



Fig. 3 (Fradkin). Genealogy chart of patient's family. The patient is the individual affected in the last generation.

blindness alone. Neither had grossly retarded hearing, but one was reported to have a "slight abnormality" in the hearing test. The affected males were all reported to have developed blindness at an early age, but none was examined in the first few months of life.

Laboratory work, including complete blood count, urinalysis, VDRL, amino acid and mucopolysaccharide screening were all negative or within normal limits, as were the chest x-ray and skull films.

During the first four months of life, the child developed a pendular nystagmus. The corneas enlarged markedly and became cloudy due to elevated intraocular pressures. The anterior chambers were obliterated. Additional vitreous hemorrhages occurred.

The boy was last seen in February, 1971, at 15 months of age. He was noted to have developed subjective entoptic stimulation by eye rubbing. Both globes had become phthisical, precluding any further fundus examination. The external appearance showed very shrunken eyes set deep in the orbits.

His developmental milestones were considered by the pediatrician to be within normal limits and there was no evidence of hearing loss.

## Comment

Norrie's disease is an X-linked syndrome of retinal malformation, mental retardation, and deafness. The clinical picture of Norrie's disease has been obtained by examining patients from eight days to 60 years of age. All affected individuals are, for all practical purposes, blind. The external examination is unremarkable. The corneas are usually clear in infancy, but during childhood develop opacities, eventually becoming opaque. In most cases, the anterior chamber is abnormally shallow or partially obliterated. Iris atrophy, ectropion uveae, as well as anterior and posterior synechiae are seen. The pupil, of course, is nonreactive. The lens is clear or slightly opaque early in the course of the process. However, cataractous changes begin early, so that by five years of age most patients have developed a true cataract.

The vitreous cavity in Norrie's disease is most unusual. A grey or greyish-yellow retrolental mass with a few vessels on its surface precludes visualization of the retina in most children. Also, the vitreous may contain hemorrhage and other opacities. In a few cases in which the retina was visible, it was partially veiled by preretinal proliferation.

The end result in adult life is a deep-set phthistic eye.

Mental retardation of varying degrees is present in 50% of these children, and progressive hearing loss occurs in one-third, beginning in childhood or later.

The description of the pathology of Norrie's disease is derived from a very few cases in which the eye had already become phthisical.

No biochemical or chromosomal abnormalities have been consistently found.

## Summary

The youngest diagnosed case of Norrie's disease, an X-linked congenital degeneration of the eye, ear, and brain, is presented. The ocular findings at birth included anisocoria, shallow anterior chambers, rubeosis iridis, retrolental vascular membranes, and vitreous hemorrhages. Subsequently, glaucoma developed and the globes became phthisical.

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# IRIDOGONIODYSGENESIS WITH CATARACT

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A variety of heritable disorders may affect the anterior segment of the eye. This report describes two brothers who show identical abnormalities of the anterior segment. These patients have anomalies of the iris and anterior chamber angle (iridogoniodysgenesis) and cataracts which developed and progressed to maturity in early adulthood. We have been unable to find reports of similar associated ocular abnormalities in the literature. The relationship of this syndrome to other inherited anterior segment anomalies is discussed.

## CASE REPORTS

This family is of Italian origin (Fig. 1). There is no history of consanguinity. The eyes of the two affected boys ($III_1$ and $III_2$) and their parents ($II_2$ and $II_3$) were examined. Data concerning other family members were obtained from the parents.

*Case* 1—This 21-year-old truck driver ($III_1$) was seen in consultation for evaluation of a cataract in his right eye and elevated intraocular pressure in his left eye. He stated that he always had poorer sight in his right eye and that recently he noted a rapid decrease in its vision. The patient denied ocular trauma or exposure to physical or chemical agents. Family history revealed that an older brother ($III_2$) had undergone cataract surgery at the age of 23 years and the mother had had repair of a retinal detachment at the age of 45 years. Medical evaluation revealed the patient to be a healthy man with a mild erythematous, scaly skin rash over his cheek bones. He was the product of a full-term pregnancy without history of maternal infection, and his growth and development were normal. Laboratory studies, including chromosomal analysis and x-rays, were normal.

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*Ocular examination*—Visual acuity was RE: 20/400 (−5.50 sph. ⊃ +2.50 cyl. ax. 90°) and LE: 20/40 (−8.00 sph. ⊃ +2.50 cyl. ax. 90°). Color vision (AO-HRR plates) was normal in the left eye. Ocular rotations were full and the eyelids and conjunctivae normal. Both corneas were normal and each measured 12 mm in diameter. Keratomer readings were: RE: 40.00 mer 5°, 40.75 mer 95°, and LE: 39.75 mer 5°, 41.75 mer 95°. Schwalbe's line was not evident on slit-lamp examination. Corectopia was present with each slightly oval pupil displaced superonasally (Fig. 2). Both irides were greyish-blue, showed scant stroma, and lacked a colarette. The pupillary ruff was absent superonasally. The periphery of each iris transilluminated. Gonioscopy revealed deep, heavily pigmented, abnormal angles (Fig. 3). A veil of pigmented tissue of varying density lined the angle from the angle recess to schwalbe's line. Normal angle structures could not be visualized. A heavily pigmented ciliary body band was apparent behind the more diaphanous portions of the abnormal angle tissue. Radial and circumferential angle vessels were present bilaterally. A moderately cataractous lens with wrinkled anterior lens capsule was present in the right eye. The left lens showed prominent cortical spokes and pigment stars on the anterior lens capsule. The right fundus was not visualized. The left fundus had an optic disk with myopic crescent and early posterior staphyloma.

The intraocular pressures (applanation) were RE: 20 mm Hg and LE: 31 mm Hg, while tonography revealed a coefficient of outflow of RE: 0.18 and LE: 0.19. Perimetry (Goldmann) showed a full left field with normal blind spot.

During a three-week observation period, the right lens rapidly matured and the capsular wrinkling increased. Follow-up tonometry showed normal intraocular pressures in both eyes. An intracapsular cataract extraction with sector iridectomy was performed and although alpha chymotrypsin (in 1: 5000 dilution) was utilized, direct zonulysis was required. Firm adhesions between vitreous and posterior lens capsule were present and were severed during delivery of the lens. There was no vitreous loss.

*Case* 2—This 26-year-old man ($III_2$) had worn glasses since early childhood. He was the product of a full-term pregnancy without history of maternal infection, and his growth and development were normal. He stated that at the age of 15 years his left eye was struck with a lead pencil. This necessitated patching for a day. At the age of 23 years, while serving in the US Navy, he noted a sudden decrease in vision in his left eye. A cataract was found and after cataract surgery he was advised that the lens "broke" during the operation.

Examination showed the patient to be well-devel-

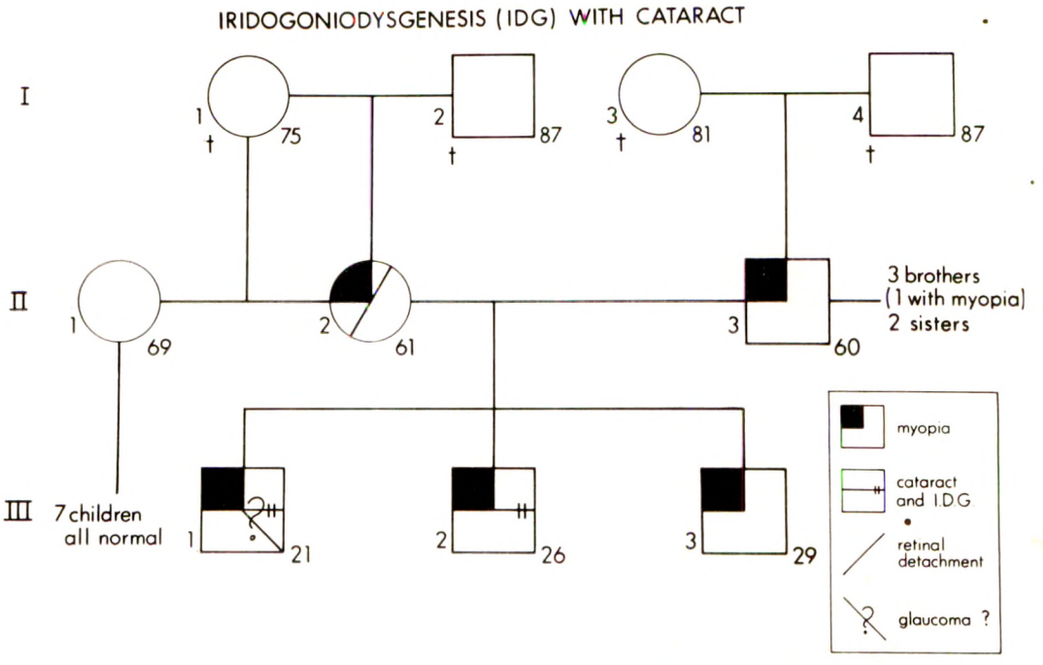



Fig. 1 (Henkind and Friedman). Pedigree of patients with iridogoniodysgenesis with cataract. The affected family members are $III_1$ and $III_2$.

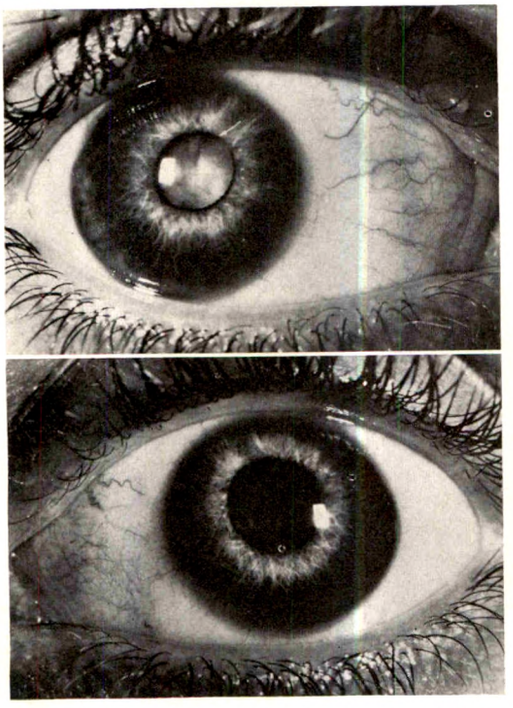


Fig. 2 (Henkind and Friedman). Case 1. Top: Right eye with iris hypoplasia, deficient pupillary ruff (arrow) corectopia and cataract. Bottom: Left eye with iris hypoplasia and cataract.

oped with no gross abnormalities except an orthodontic problem which was being corrected by braces.

*Ocular examination*—The eyes of this patient were strikingly similar to those of his brother ($III_1$). Visual acuity was RE: 20/25 (plano sph. ⊃ +1.00 cyl. ax. 90°) and LE: 20/30 (+6.75 sph.). Color vision (AO-HRR plates) and Amsler Grid testing were normal in each eye. The intraocular pressures (applanation) were 11 mm Hg. Ocular motility, eyelids and adnexae were normal. Both corneas were clear except for peripheral scar-

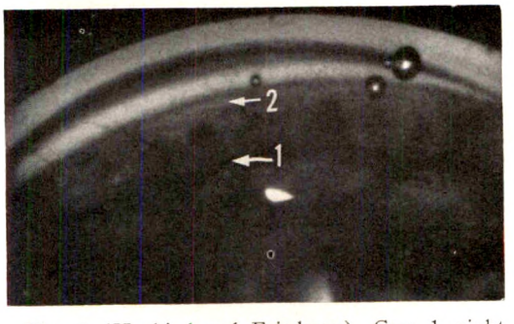



Fig. 3 (Henkind and Friedman). Case 1, right eye. Goniophotograph of angle at six o'clock (Goldmann gonioprism). Arrow 1 points to line of iris insertion. Arrow 2 points to Schwalbe's line. The area between 1 and 2 is lined by a veil of pigmented tissue of varying density. Note the diaphanous areas between the arrows.

ring superiorly and a superficial central scar in the left eye. In the right eye, Schwalbe's line was barely visible nasally on slit lamp examination. Horizontal corneal diameters were RE: 12 mm, and LE: 11 mm. Keratometer readings were: RE: 40.75 mer 5°, 43.00 mer 95°, and LE: 41.50 mer 180°, 41.75 mer 90°, with irregular mires. Corectopia was present with each slightly oval pupil displaced superonasally (Fig. 4). Both irides were greyish-blue, showed scant stroma, and lacked a collarette. There was absence of the pupillary ruff superonasally in both eyes. The periphery of each iris transilluminated. In the left eye, a basal iridectomy was present at 10 o'clock and a slit-like opening at 12 o'clock. Gonioscopy was virtually identical to that seen in his brother. Both angles were deep, heavily pigmented, and lined by a veil of abnormal tissue (Fig. 5). There were prominent radial and circumferential angle vessels in both eyes. After iris dilatation, the right lens was noted to have numerous pigment stars on the anterior capsule and a relatively dense posterior subcapsular opacity. Vitreous floaters were present in the right eye. The right fundus appeared normal. Examination of the left fundus revealed an optic disc with myopic conus.

*Case* 3—This 61-year-old housewife is the mother of both patients ($III_1$ and $III_2$). She has worn a myopic correction since childhood. In January, 1956, she underwent surgery for a retinal detachment in her right eye. There is no history of ocular trauma or infection and her general health is excellent.

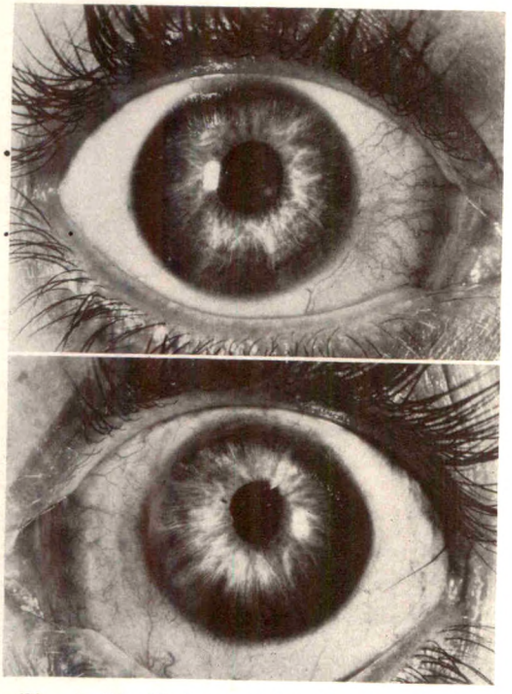


Fig. 4 (Henkind and Frieman). Case 2. Top: Right eye with iris hypoplasia and corectopia. Bottom: Left eye with peripheral iridectomy at 10 o'clock, iris hypoplasia and corectopia.

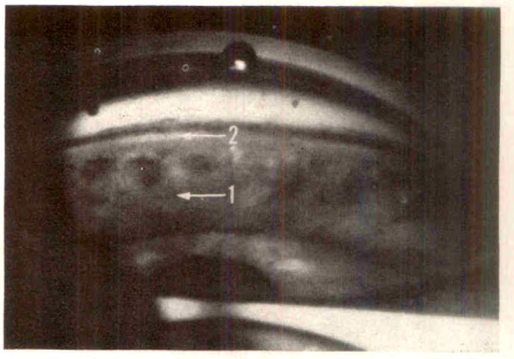



Fig. 5 (Henkind and Friedman). Case 2, right eye. Goniophotograph of angle at six o'clock (Goldmann gonioprism). Arrow 1 points to line of iris insertion. Arrow 2 points to Schwalbe's line. As in Figure 3, the area between 1 and 2 is lined by a veil of pigmented tissue. Note the diaphanous zones between the arrows.

*Ocular examination*—Visual acuity was RE: hand motion only (−4.25 sph.), and LE: 20/40+ (−5.50 sph.). Color vision (AO-HRR plates) was normal. The intraocular pressures (applanation) were 12 mm Hg. Ocular rotations were full and the eyelids and conjunctivae normal. The corneas were normal and both diameters measured 11 mm. Both irides were hazel and displayed a normal collarette and pupillary ruff. The pupils were centric, reactive to light and 4 mm in diameter. Gonioscopy revealed wide open angles (3+) with a normal configuration. Slight pigment speckling was present overlying the meshwork especially inferiorly. The lenses showed early cortical changes, more so in the right eye. Vitreous floaters were seen in the right eye. The right fundus displayed a number of pigmented chorioretinal scars in the inferotemporal quadrant and a retinal band nasally. The left fundus was normal.

*Case* 4—This 60-year-old man is the father of both patients ($III_1$ and $III_2$). He denies any ocular complaints and is in excellent health.

*Ocular examination*—Visual acuity was RE: 20/25 (−2.00 sph. ⊃ −0.50 cyl. ax. 160°) and LE: 20/60+ (−2.75 sph. ⊃ −0.50 cyl. ax. 165°). The intraocular pressures (applanation) were 14 mm Hg. Ocular motility, eyelids and conjunctivae were normal. The corneas were normal and both corneal diameters measured 10 mm. Both irides were hazel and displayed normal markings; the pupils were centric, reactive to light and 4 mm in diameter. Gonioscopy revealed open angles (3+) with a normal architecture. A prominent circular vessel was seen in the right chamber angle. The lens showed early cortical opacities inferonasally in each eye. The fundi were normal.

## Discussion

These two brothers display an unusual

combination of ocular findings: iridogoniodysgenesis and rapidly maturing cataracts. Three major points are to be considered: the genetic aspects of the condition, the relation of this syndrome to other anterior segment anomalies, and the early appearance of cataracts.

The occurrence of an almost identical clinical picture in two brothers suggests an hereditary etiology. Both were healthy from birth without stigmata or prenatal infection. The normal appearance of the parents' anterior ocular segments, and the absence of a family history of cataract during the preceding two generations, are strong evidence against autosomal dominant inheritance. Sex-linked recessive inheritance is doubtful because the maternal grandfather presumably had normal eyes and the mother's eyes are unlike those of her affected sons. We must consider, therefore, that iridogoniodysgenesis and early cataract formation is an expression of autosomal recessive inheritance. Further evidence for this is the striking similarity of the affected brothers' eyes. In this regard, recessive conditions often present a limited range of expressivity while dominant ones have a variable phenotype.[1]

The relation between the present condition and other anterior segment anomalies is summarized in Table 1.

The posterior embryotoxon of Axenfeld[2] consists of a prominent Schwalbe's line which can be seen by direct observation without gonioscopy. A prominent Schwalbe's line is present in about 15% of all individuals.[3] In more pronounced cases of posterior embryotoxon, the iris may be hypoplastic and adhesions between the corneal opacity and the peripheral iris stroma may occur. Such cases probably represent variants of Rieger's anomaly. Dominant pedigrees, particularly where there is involvement of the iris, have been reported, but autosomal recessive inheritance has also been documented.[4] Cataract formation is not a feature of this condition. One of our patients ($III_2$) has an externally visible posterior embryotoxon in his right eye, but we do not feel that it is a characteristic of this syndrome.

Mesodermal dysgenesis of the iris and cornea is an anomaly that was clearly delineated by Rieger.[5] Its primary features are hypoplasia of the anterior iris stroma, iris strands bridging the angle and posterior embryotoxon. Glaucoma is common in the first few decades of life and a variety of lens opacities have been noted, but early onset of cataract has not been described.[6] Rieger's anomaly is inherited as an autosomal dominant and a wide range of expressivity is evident in affected families. When associated with dental or skeletal anomalies, the condition has been termed Rieger's syndrome. Our affected patients can be separated from those with Rieger's anomaly both by the different clinical appearance of the eyes and by the presumably different mode of inheritance.

Peters' anomaly,[7] considered a mesoder-

TABLE 1

COMPARISON OF THE HERITABLE ANTERIOR SEGMENT ANOMALIES

| Condition | Heredity | Ocular Abnormalities | | | | | Other Findings |
|---|---|---|---|---|---|---|---|
| | | Cornea | Iris | Angle | Lens | Glaucoma | |
| Posterior embryotoxon[2-4] | Recessive(?) dominant(?) | Common | Occasional* | Occasional* | None | Occasional* | None |
| Mesodermal dysgenesis of iris and cornea[5,6] | Autosomal dominant | Common | Common | Common | Occasional* | Common | May have dental or skeletal abnormalities |
| Peters anomaly[7,8] | Recessive(?) | Common | Common | Common | Common | Common | None |
| Goniodysgenesis with glaucoma[10,11] | Autosomal dominant | Occasional* | Common | Common | None | Common | None |
| Iridogoniodysgenesis and cataract (present cases) | Autosomal recessive | None | Common | Common | Common | ? | None |

* Involvement has been noted.

mål dysgenesis of the cornea,[8] is a congenital disorder in which there is a central corneal opacity with abnormalities of the deep stroma and a local absence of Descemet's membrane. Though the anomaly may be limited to the cornea, various defects in the anterior segment, including corectopia, iris hypoplasia, persistant pupillary membranes, and anterior polar cataract have been recorded.[8] While there are human pedigrees with combinations of Rieger's and Peters' anomalies, the latter is generally considered to involve recessive inheritance.[8] On the other hand, Reese and Ellsworth[9] have classified the various anterior segment conditions together under the broad title, anterior chamber cleavage syndrome, and have noted that mothers of a number of their patients had rubella or other presumably viral infections during the first trimester of pregnancy.

Goniodysgenesis and hereditary juvenile glaucoma[10] is characterized by an abnormal iridocorneal angle, iris hypoplasia, and glaucoma which develops in the first few decades of life. Inheritance is autosomal dominant in nature. The iris hypoplasia, corectopia, and appearance of the angles in this condition are very similar to that found in our patients. One of our patients ($III_1$) had several elevated intraocular pressure readings in his left eye, but tonography, visual fields, and repeat applanation tonometry failed to confirm the presence of glaucoma. It is conceivable that elevated ocular tensions will be manifest as glaucoma at a later date. In the large pedigree reported by Jerndal[10] and that of Weatherill and Hart[11] a number of family members had "minor" dysgenesis of the angle and normal ocular pressure. Early onset of cataract was not noted in either of these pedigrees, nor is it a feature of congenital glaucoma, with the possible exception of that seen with rubella. While our patients resemble those with goniodysgenesis and juvenile glaucoma, the presence of cataracts, lack of glaucoma, and different mode of inheritance are significant distinguishing characteristics.

We presume that the early appearance and maturation of cataracts in our cases are related to the anterior segment abnormality. The possibility does exist, however, that the lens changes are unrelated to the iris and angle changes. A number of heritable conditions are characterized by the early appearance of rapidly progressive cataracts. Werner's syndrome[12] is one such disorder, with cataracts developing between the ages of 20 and 35 years and rapidly progressing to intumescence. The premature senility and endocrine disturbances of Werner's syndrome were not present in our cases. The cataracts found in Rothmund's syndrome develop in the first few years of life. Neither Werner's nor Rothmund's syndromes have associated angle anomalies. Rapidly maturing cataracts are also seen in association with diabetes mellitus. Neither of our affected patients manifested chemical or clinical evidence of diabetes. Patient $III_1$ had a very mild eczematoid eruption overlying his malar prominences. There were no other skin lesions and therefore one cannot relate the cataracts to a dermatologic disorder. Neither affected patient was ever treated with x-radiation nor were they exposed to the wide variety of chemical agents which have been reported to induce cataracts.[12] Conradi's syndrome (dysplasia epiphysealis punctata) has recently been reported to have an anterior chamber angle anomaly similar to that found in mesodermal dysgenesis.[13] Patients with this condition also have cataracts. Our patients lack the typical clinical appearance of patients with this syndrome. Pigmented lens capsule stars were present on the anterior capsule of the less cataractous lens of each affected brother and represents remnants of a persistant pupillary membrane. Such remnants are not usually associated with cataract formation and are commonly seen in otherwise normal eyes.[14]

## Summary

Two brothers manifested abnormalities of the iris and anterior chamber angle (iridogoniodysgenesis) and cataract. The cataracts developed in early adulthood and rapidly progressed to maturity. The absence of a

family history of cataract during the preceding two generations, and the normal appearance of the parents' anterior ocular segments, provided strong evidence against autosomal dominant inheritance.

ACKNOWLEDGMENTS

We thank Dr. Herbert Vogel for referring his patient for our observation. We also thank Miss Leslie Rosenberg for typing the manuscript and Mr. Henrick Malpica for the photographs.

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# CATARACTS IN THE SMITH-LEMLI-OPITZ SYNDROME

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A constellation of phenotypic anomalies are present in the Smith-Lemli-Opitz syndrome: (1) microcephaly with narrow transverse diameter of the cranial vault, (2) broad maxillary alveolar ridge, (3) short nose with anteverted nares, (4) micrognathia, (5) polydactyly and syndactyly of the second and third toes, (6) hypospadias and cryptorchidism (male pseudohermaphroditism), (7) mental retardation, and (8) congenital pyloric stenosis. Four children with the Smith-Lemli-Opitz syndrome were initially described in 1964.[1] Eleven additional children have been reported since,[2-6] but none in the ophthalmic literature. The pediatric reports included brief descriptions of the eyes; cataracts were noted in two such patients.[4,6] A child with Smith-Lemli-Opitz syndrome and cataracts who underwent successful cataract surgery is described here.

## CASE REPORT

At the time of this report, this boy was eight years old (Figs. 1 and 2). His eyes were examined on repeated occasions, twice under general anesthesia. He was born March 1, 1962, to apparently healthy parents. The mother (age 22) had experienced four spontaneous abortions prior to his birth. There was, however, no history of familial diseases or consanguinity. Gestation lasted 40 weeks and the only recorded illness was a "skin rash" during the second trimester of pregnancy. Her medications during the pregnancy included occasional injectable calcium and iron prescribed by the obstetrician.



Fig. 1 (Cotlier and Rice). Catatonic position of child with Smith-Lemli-Opitz syndrome.



Fig. 2 (Cotlier and Rice). Typical facies of child with Smith-Lemli-Opitz syndrome. Note narrow transverse diameter of the cranial vault, short nose and anteverted nares, low-set ears, slight antimongoloid slant of eyes, meeting of eyebrows at the midline.

At birth, the child weighed six pounds and two ounces. From his birth, he fed poorly, and at the age of 29 days he was admitted because of frequent vomiting without diarrhea. Examination at that time revealed marked dehydration. His weight was five pounds and five ounces. There was poor head control, marked inactivity, poor sucking ability. He showed simian creases. There was a 2 cm phalloclitois bound by a chordae in which the urethra was not identified (Fig. 3). He had bilateral polydactyly, syndactyly of the second and third toes (Fig. 4), and talipes calcaneovalgus.

Laboratory tests showed the complete blood count to be within normal limits. White blood cells were numerous (too numerous to count); other blood chemistries were normal. Urine culture revealed Aerobacter cloacae sensitive to kanamycin. Urinalysis was otherwise normal, including 17-ketosteroids. An intravenous pyelogram and electrocardiogram were normal. X-ray examination showed the long bones to be normal and appropriately developed for his chronological age. An upper gastrointestinal series revealed pyloric stenosis. Buccal smear revealed a chromosomal male (3% Barr bodies).

Intramuscular kanamycin 35 mg every 12 hours

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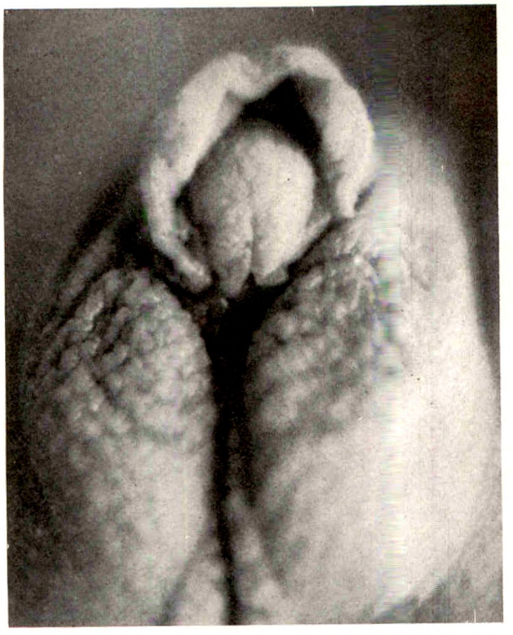


Fig. 3 (Cotlier and Rice). Pseudohermaphrodite genitals, hypospadias.

and intravenous fluids cleared the urinary tract infection. Because of the protracted vomiting and the pyloric stenosis, a Ramstedt pyloroplasty was performed on April 7; and this was followed by a gastrostomy on April 30. The patient regained his birth weight on May 20, at which time he was discharged. At three months of age (10 days later), the child had gained seven ounces (weight: six pounds and nine ounces). He smiled and was able to fixate with both eyes. Head circumference was 40.5 cm.

At six months of age, ocular fixation was absent, and at 10 months of age bilateral cataracts were noted. Ophthalmic evaluation on January 21, 1963, revealed bilateral anterior cortical lens opacities and iris synechiae to the lens. There was bilateral pendular nystagmus and esotropia. He was admitted for cataract surgery of the right eye. Blood chemistries at that admission revealed normal CBC, urinalysis, VDRL, Kahn, and Wasserman, and no galactosuria.

*Cataract surgery*—Under general anesthesia, a 1% lidocaine retrobulbar injection was given. A superior rectus 4-0 silk suture was placed in the right eye. A fornix-based flap was dissected and two 6-0 chromic gut sutures were preplaced in a limbal groove extending from 10 to 12 o'clock. A keratome incision was made and the anterior chamber entered. The wound was enlarged with corneoscleral scissors to 120 degrees. A full iridectomy, capsulotomy, and irrigation of lens material followed. The preplaced sutures were tied, leaving a 5 mm air bubble in the anterior chamber.

The postoperative course was uneventful. Mydriatics were applied topically once a day. Postoperative retinoscopy was +13.00 sph. ⊃ +2.50 cyl. ax 90°. Fundus details were easily visualized in the operated eye.

Aphakic glasses were prescribed, but in following visits it was noted that he did not wear them. Because of his mental retardation and absent speech, visual acuity could not be determined.

In September, 1970, the patient was re-admitted to the University of Illinois Eye and Ear Infirmary for ophthalmoscopy of the right eye and evaluation of the fundus and the cataract in the left eye (Fig. 5).

X-ray films on this admission revealed a skull small for the patient's age with prominent convolutions. The extremeties showed osteoporosis suggestive of disuse and muscle wasting, and an extra epiphysis at the proximal end of the second metacarpal. Complete blood count, urinalysis, serum calcium, phosphorus and serum protein electrophoresis were normal. Karyotype in peripheral leukocytes was normal. Urine amino acid analysis (Table 1) was within normal limits. Rubella antibody titer in serum was 1 : 16.

The eye examination revealed 40 prism diopters of constant left esotropia, an antimongoloid slant, and brows meeting at the midline, but no blepharoptosis. The conjunctivae and corneas were unremarkable. The anterior chamber of the right eye was



Fig. 4 (Cotlier and Rice). Syndactyly of the second and third toes.

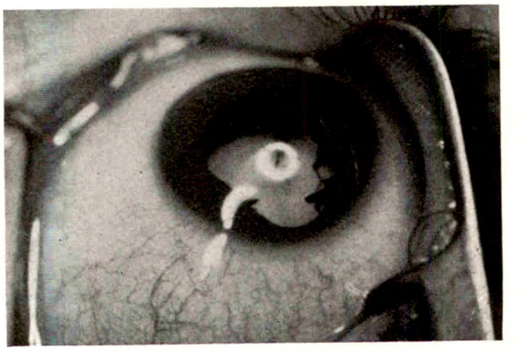


Fig. 5 (Cotlier and Rice). Left eye: Mature and partially resorbed cataract and posterior synechiae.

TABLE 1

URINE CHROMATOGRAPHY*

| | Normal Percentiles | | | Present Case |
|---|---|---|---|---|
| | 25% | 50% | 75% | |
| Glutamic acid | 6 | 13 | 26 | 21 |
| Serine | 25 | 49 | 81 | 20 |
| Glycine | 38 | 60 | 95 | 62 |
| Threonine | 14 | 32 | 50 | — |
| Alanine | 31 | 44 | 64 | 30 |
| Glutamine | 40 | 61 | 92 | 27 |
| Valine | 4 | 7 | 15 | — |
| BAIB | 5 | 9 | 19 | 58 |
| Lysine | 15 | 32 | 53 | 31 |
| Tyrosine | 12 | 17 | 31 | 15 |
| Taurine | 5 | 10 | 19 | 40 |
| Methyl histidine | | 22 | | 60 |
| Cystine | | 37 | | 82 |
| Arginine | | 11 | | — |
| Phenylalanine | 10 | 19 | 28 | — |
| Leucine | 4 | 7 | 12 | 12 |
| Proline | | 10 | | — |
| Homocitrulline | | 5 | | — |
| Histidine | | 102 | | 175 |
| Phenolic acids | | | | Normal |
| Organic acids | | | | Normal |
| Chondroitin sulphate | | | | Negative |
| Other | | | | |
| Creatinine | | | | 99 mg% |
| Keto acid | | | | Faint positive |

* Amino acid excretions are expressed as μg/ml urine.[7]

clear and of aphakic depth. An iridectomy was present and the pupil was free of lens material (Fig. 6). The fundus revealed a normal disk, vessels and macular area. By indirect ophthalmoscopy, the retinal periphery was normal in the right eye. The left eye showed a mature, partially resorbed cataract with iris synechiae to the lens (Fig. 5). Normal retinal vessels and choroidal architecture could be seen around the nasal side of the cataractous lens. The vitreous appeared clear and normal in both eyes. Schiøtz tensions were 18.9 mm Hg in the right eye and 12.6 mm Hg in the left eye. Gonioscopy revealed wide open angles without anomalies in both eyes.



Fig. 6 (Cotlier and Rice). Aphakic right eye and cataractous left eye.

## DISCUSSION

An excellent summary of the first 13 cases with Smith-Lemli-Opitz syndrome is found in the report by Park and associates.[4] We tabulated the data reported in patients with the Smith-Lemli-Opitz syndrome (Tables 2 and 3), including the two most recently reported cases[5,6] and the present one, and analysis disclosed several factors of interest. There is a higher incidence of the Smith-Lemli-Opitz syndrome in males (male:female ratio 4:1). All Smith-Lemli-Opitz babies have had a normal gestation period and all parents were young (in the 20- to 30-year bracket). Most (10 out of 16) were first or second babies in the obstetrical order. Birth weights and lengths of infants with the Smith-Lemli-Opitz syndrome cases were slightly below, but still within normal limits, and all had a history of retarded growth, failure to thrive, and mental retardation. Repeated vomiting

TABLE 2

INCIDENCE* OF HISTORICAL FINDINGS AND CLINICAL SIGNS IN 16 REPORTED CASES

| Finding | No. Studied | No. Positive | % of Those Reported |
|---|---|---|---|
| Historical data: | | | |
| Parental age range | | | |
| Mothers: 21 to 28 years | | | |
| Fathers: 22 to 33 years | | | |
| Parity of mothers at this birth: | | | |
| Primaparous (4) | | | |
| 2 (5) | | | |
| 3 (5) | | | |
| 4 (2) | | | |
| History of abortion | 16 | 8 | 50 |
| Breech delivery | 16 | 6 | 37.5 |
| Normal period of gestation (range 38 to 43 weeks) | 14 | 13 | 92 |
| No. males | 16 | 13 | 81 |
| No. low birth weights (range 3.8 to 6 pounds) | 16 | 0 | 100 |
| No. below normal length (range 17 to 21 inches) | 16 | 0 | 100 |
| Clinical signs: | | | |
| Failure to thrive | 15 | 15 | 100 |
| Vomiting | 9 | 13 | 70 |
| Growth retardation | 14 | 14 | 100 |
| Mental retardation | 15 | 15 | 100 |
| Microcephaly | 16 | 16 | 100 |
| Anteverted nares | 13 | 13 | 100 |
| Low-set ears | 9 | 13 | 70 |
| Epicathal folds | 6 | 9 | 66 |
| Blepharoptosis | 11 | 13 | 85 |
| Strabismus | 8 | 12 | 66 |
| Micrognathia | 12 | 12 | 100 |
| Muscular tone | | | |
| Increased | 14 | 7 | 50 |
| Normal | 14 | 2 | 14 |
| Decreased | 14 | 5 | 35 |

* Given in % of those examined.

TABLE 3

INCIDENCE* OF CLINICAL AND LABORATORY ABNORMALITIES IN 16 REPORTED CASES

| Finding | No. Studied | No. Positive | % of Those Reported |
|---|---|---|---|
| Clinical findings: | | | |
| Broad maxillary alveolar ridge | 12 | 10 | 83 |
| Cleft palate or bifid uvula | 10 | 7 | 70 |
| Hypospadias | 13 | 12 | 92 |
| Cryptorchidism | 13 | 11 | 85 |
| Horizontal or bridged upper palmar crease | 12 | 11 | 92 |
| Whorl patterns (10/10) | 9 | 4 | 44 |
| Distal placed arial triradius | 11 | 6 | 54 |
| Short thumb and/or big toe | 10 | 4 | 40 |
| Cutaneous syndactyly of second and third toes | 16 | 13 | 81 |
| Deep pit anterior to anus | 8 | 5 | 62.5 |
| Laboratory findings: | | | |
| Normal chromosome analysis | 12 | 12 | 100 |
| Abnormal intravenous pyelogram | 10 | 6 | 60 |
| Abnormal electroencephalogram | 4 | 4 | 100 |

* Given in % of those examined.

due to pyloric stenosis was reported in 70%. Microcephaly, micrognathia, and anteverted nares were found in 100% of the patients. Slightly less frequent findings were low-set ears slanted away from the eyes; epicanthal folds, blepharoptosis, and strabismus; broad maxillary alveolar ridge and cleft palate or bifid uvula. Genital anomalies (consisting of hypospadias and cryptorchidism) were frequently present, and syndactyly or polydactyly were perhaps the most distinct diagnostic signs of the syndrome; palmar and finger anomalies were less frequently seen.

Laboratory studies have failed to uncover a metabolic or chromosomal defect responsible for the Smith-Lemli-Opitz syndrome. Our patient had a normal chromosomal pattern (46, XY) in cells derived from the culture of peripheral leukocytes. Chromosomal analyses were normal in all 12 Smith-Lemli-Opitz syndrome cases in which karyotype studies were made.

Thus far, only one generation has been involved. The presence of affected siblings and the high incidence of maternal abortions would indicate a genetic pattern not compatible with orthodox dominant inheritance or sporadic mutation. Because of the high incidence of affected males, it has been suggested that the syndrome may be lethal to females, who are eliminated by abortion (an X-linked dominant mutation).[1] Park and his co-workers analyzed the sex distributions of siblings of male propositi.[4] Two of six males

and two of six females were affected, thus eliminating the possibilities of sex segregation. In fact, these authors believe an autosomal recessive mode of inheritance is most probable, although an environmental factor cannot be eliminated. History of consanguinity has been absent from families of Smith-Lemli-Opitz syndrome patients. Further studies on the genetics of the Smith-Lemli-Opitz syndrome are needed to clarify this complex presentation pattern.

The association of cataracts and pseudohermaphroditism is unique and found only in the Smith-Lemli-Opitz syndrome. Polydactyly, the facial features, and mental retardation are not exclusive to the Smith-Lemli-Opitz syndrome. Thus, the differential diagnosis[8] of these congenital cataracts is as follows:

*With poly- or syndactyly*—Down's syndrome (also with duodenal obstructions); 13-15 trisomy and 18-trisomy (75% death rate within the first six months of life); chondroectodermal dysplasia (Ellis-van Creveld syndrome); De Lange syndrome, Cockayne's syndrome, Turner's syndrome, Lawrence-Moon-Biedl syndrome, achrocephalosyndactyly (Apert's syndrome).

*With mental retardation*—Miller's syndrome (aniridia, Wilms' tumor), mannosidosis, Cockayne's syndrome, Lowe's syndrome, galactosemia, congenital rubella.

Two other Smith-Lemli-Opitz patients with cataracts have been recorded. The five-year-old patient of Park and co-workers[4] had congenital heart disease "compatible with tetralogy of Fallot" and a cataract in the left lens evident only on slit-lamp examination, but the type was not described. The eight-year-old patient with Smith-Lemli-Opitz syndrome described by Finley and associates[6] had bilateral cataract surgery, but the type of cataract and surgical result was not stated.

The surgical removal of mature cataracts is nearly always indicated. However, in patients with cataracts, CNS degeneration, and mental retardation, the visual prognosis may not be dramatically changed by such surgery. It is to be hoped that research in genetics, chromosomal defects, and in enzyme deficiency in the coming decades may make cataract extractions in such children more meaningful.

## Summary

Successful cataract surgery was performed in a child with the Smith-Lemli-Opitz syndrome. Clinical signs included microcephaly, short nose with anteverted nares, polydactyly, syndactyly of the second and third toes, mental retardation, male pseudohermaphroditism, and congenital pyloric stenosis. Chromosomal studies were normal in this child, and in all 12 of those in whom such studies were performed among 15 previously reported cases. In the case described, and others described earlier, this syndrome does not conform to any known human genetic inheritance pattern.

## Acknowledgment

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# SYMPATHETIC OPHTHALMIA AND LYMPHOCYTE TRANSFORMATION

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There is considerable evidence to suggest that lymphocytic transformation in vitro is an immunologic response. Since this reaction was shown to be related to an antigen to which a patient is selectively sensitized, interest has turned to the possible roles it may play in the interaction of immunity and disease. Enhanced reactivity to homologous tissue antigens is demonstrable in patients afflicted with diseases of alleged autoimmune mechanisms.[1-16]

Sympathetic ophthalmia is felt by many to represent a form of hypersensitivity to uveal tissue following a perforating injury to one eye. Although convincing evidence is still lacking, there are a number of reports which lend support to the role of hyperimmunity in the pathology of this ocular clinical entity.[17-22]

To the best of our knowledge, the in vitro lymphocytic reaction in sympathetic ophthalmia was not previously reported. This is a report of the stimulation of peripheral blood lymphocytes with soluble extract of homologous uveal-retinal tissues in histologically proven cases of sympathetic ophthalmia.

## MATERIAL AND METHODS

Eight patients with histologically proven sympathetic opthalmia were selected for study from the ophthalmology service of the National Eye Institute. Each patient was referred to the Institute because of progression of disease in his remaining eye. All were previously treated or maintained on corticosteroids. Patients 1, 6, and 8 had also been on immunosuppressive methotrexate.

Control studies were performed on patients from the same facility with active ocular diseases other than sympathetic ophthalmia as well as from a normal volunteer.

Blood was drawn 48 hours after the last dose of all medications into a heparinized syringe (20 units/1 ml blood) and allowed to stand between one to three hours at room temperature for RBC sedimentation. The blood was centrifuged in an IEC centrifuge at 450 rpm for 30 seconds and advanced immediately to 1000 rpm before the machine was turned off. The plasma and buffy coat were aspirated and cells were adjusted to $1 \times 10^6$/ml with Eagle's basal 199 medium containing penicillin and streptomycin. The cell mixture was aerated with 95% oxygen and 5% $CO_2$ and 6 ml aliquots were placed into 25 ml tissue culture bottles. Antigens (uveal-retinal preparation) were added in concentration of 500 and 1000 λ along with appropriate controls of human muscle extract of the same concentrations and phytohemagglutinin (PHA). Cultures were incubated at 37°C for five days.

### PREPARATION OF SLIDES FOR BLAST TRANSFORMATION

After five days of incubation, the cells were transferred into a 40-ml conical tube and centrifuged at 500 to 700 rpm for five to seven minutes. The supernatant was discarded; the cell button was resuspended and dispersed through vigorous shaking. The latter was fixed by slowly adding freshly prepared modified Carnoy's solution (8 methyl alcohol: 1 glacial acetic acid) for 10 minutes. The cell suspension was centrifuged again and the supernatant discarded. The cell button was dispersed by shaking and 0.5 to 1.0 ml freshly made Carnoy's fixative was again added resulting in a slightly cloudy suspension. A few drops of the latter was placed on a clean glass slide and allowed to air dry. The cells were subsequently stained with

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Giemsa or other Romanowsky stains in the usual manner. Examination was under oil immersion and 1000 continuous cell count was made for each slide. Each slide was coded and remained unknown to the examiner until all preparations were read.

Since the study began in 1963, to insure the uniformity of methodology, lymphocytic transformation continued to be determined by light microscopy, in preference to the more sensitive radioactive incorporation methods.

### Preparation of soluble tissue extract

*Uveal-retinal antigen(s)*—Approximately 10 g of human uveal-retinal tissues (obtained from a local eye bank) was homogenized in two volumes of pH 7.6 buffer containing: 0.35M sucrose, 0.004M $MgCl_2$, 0.025M KCl, and 0.05M TRIS. The homogenate was centrifuged for 30 minutes in a Beckman ultracentrifuge, Model L-2 with a titanium No. 50 rotor. The supernatant was decanted with a Pasteur pipette and brought to 100% saturation with ammonium sulfate (6.97 g for every 10 ml of sucrose extract); ammonium sulfate was slowly introduced in the already mixing sucrose extract, and allowed to continue mixing in ice for 30 minutes. The solution was again centrifuged for 30 minutes. The clear supernatant was discarded and the pellet was resuspended in 0.05M phosphate buffer, pH 7.4. The suspension was then dialyzed against two liters of the same buffer three times at one hour, six hours, and eight hours. The final concentration of the dialyzed contents was adjusted to 10 mg/ml as determined by the standard procedure according to Lowry.

*Human muscle antigen(s)*—Striated muscle was obtained at autopsy from the quadraceps and the soluble extract was prepared in the same manner as the uveal-retinal tissues. The final total protein concentration was adjusted to 10 mg/ml.

## Results

The transformed lymphocyte is a large cell which has deeply basophilic, nongranular cytoplasm surrounding a rounded nucleus which contains homogeneously staining chromatin and prominent nucleoli (Fig. 1). In the cytoplasm there is often a highly stained area bordering one side of the nucleus. In addition, there are often several small, unstained cytoplasmic vacuoles. The diameter of the largest cells may be three times that of a small lymphocyte. Smaller blastoid cells, intermediate in size between these very large cells and the small lymphocyte are also present. Many, but not all, of the blastoid cells are found aggregated in clusters. Mitotic division as a result of blastogenetic activity is regularly seen.[23]

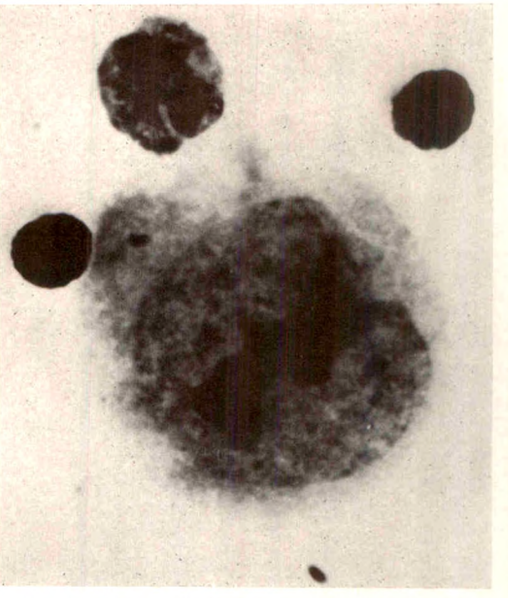


Fig. 1 (Wong, Anderson, and O'Brien). Large cell is typical of lymphoblast after undergoing transformation from small lymphocyte. Intermediate-sized blast cell and small lymphocytes are also seen (Giemsa, ×480).

In the present study, all but one of the patients with active sympathetic ophthalmia demonstrated enhanced lymphocytic transformation in the presence of homologous human uveal-retinal extract (Table 1). The mean blastogenic enhancement showed a 10-fold increase (55.5) in the presence of uveal-retinal extract when compared to its own control incubated in the absence of ocular antigens (5.6). In the control group of

TABLE 1

DATA FROM EIGHT PATIENTS WITH SYMPATHETIC OPHTHALMIA

| Patient* Age and Sex | Duration of Disease | Blast Transformation (per 1000 cell counted) | | |
|---|---|---|---|---|
| | | Control | Ocular Antigens (1000 λ) | PHA |
| 43—M | 2 years | 2 | 189 | 436 |
| 14—M | 7 years | 4 | 51 | 301 |
| 10—M | 6 months | 2 | 47 | 373 |
| 42—F | 18 years | 7 | 39 | — |
| 16—M | 5 years | 4 | 47 | 368 |
| 55—M | 6 years | 17 | 34 | 504 |
| 18—M | 4 years | 5 | 33 | — |
| 9—M | 1 month | 4 | 4 | 289 |
| Mean values | | 5.6 | 55.5 | 378 |

* All patients were Caucasians.

patients without sympathetic ophthalmia, there was no significant increase in lymphocytic transformation (Table 2). The mean values were identical (13.6 vs 17.3). The increase in blastogenesis in the sympathetic ophthalmia group is significant ($P<0.05$) (Table 3).

The sympathetic ophthalmia patient with the highest degree of transformation manifested the least clinical evidence of active disease. The anterior segment was entirely free of inflammatory activity and the media into the fundus were clear. He had extensive multifocal areas of chorioretinal atrophy which corresponded to large Dalen-Fuch nodular formations in the histopathology of the enucleated eye. The only control patient who showed a twofold enhanced blastogenesis was a 14-year-old girl with presumed Vogt-Koyanagi-Harada's disease.

The human uveal-retinal preparation used in this study contained up to six antigenic components as determined by diffusion precipitin immunoelectrophoresis using several preparations of rabbit antihuman-uveal-retinal antisera (unpublished observation). The

TABLE 2

DATA FROM SEVEN CONTROL PATIENTS

| Patient, Age, Sex, and Color | Name and Duration of Disease | Blast Transformation (per 1000 cell counted) | | |
|---|---|---|---|---|
| | | Control | Ocular Antigens (1000 λ) | PHA |
| 27—M(W) | Normal, no eye disease | 5 | 6 | 418 |
| 78—F(W) | Bullous keratopathy, five years | 52 | 55 | 502 |
| 71—M(W) | Chronic simple glaucoma, five years | 9 | 7 | 382 |
| 64—M(W) | Presumed histoplasmic chorioretinitis, 11 years | 11 | 16 | 312 |
| 18—M(W) | Behçet's disease, one year | 2 | 1 | 489 |
| 57—F(N) | Toxoplasma chorioretinitis, two months | 5 | 4 | — |
| 14—F(N) | Vogt-Koyanagi-Harada syndrome, four years | 11 | 32 | 366 |
| Mean values | | 13.6 | 17.3 | 411 |

TABLE 3

INCREASE IN BLASTOGENESIS IN THE PRESENCE OF UVEAL-RETINAL EXTRACT IN PATIENTS AND CONTROLS

| Group | Control Sera | Enhancement | Average Increase in Enhancement* |
|---|---|---|---|
| Patients | 5.6 | 55.5 | 49.9 |
| Controls | 13.6 | 17.3 | 3.7 |

* Significant at $P < 0.05$ level.

concentration of antigen giving rise to the best degree of enhancement in each patient showing blastogenesis appears to be 1000 λ (consisting of 10 mg/ml total protein).

The lymphocytes from all patients tested were markedly stimulated when incubated with PHA. The mean percentage of cells affected for the sympathetic ophthalmia group was 37.8% and for the control group 31.1%.

## DISCUSSION

The cellular and chemical reactions seen with in vitro stimulation of blood lymphocytes have been reported with numerous stimuli to induce these cellular changes.[1-16,24-33] The enhancement is quantitated by determining the percentage of transformed cells by microscopy or by the radioactive precursors of DNA, with subsequent measurement of the incorporation by the blastoid or transformed cells.[1,26]

Our data show enhanced lymphocytic transformation of patients with sympathetic ophthalmia when their peripheral leukocytes were exposed to homologous uveal-retinal antigens. The reaction appears to be specific, since control cultures containing homologous skeletal muscle antigens failed to evoke any significant degree of response. The present study indicates, in the light of our present knowledge, that patients with clinically active sympathetic ophthalmia contain sensitized lymphocytes to some component or components of uveal-retinal antigen(s). The ability of lymphocytes to transform in the presence of the sensitizing antigen involves the conditioning of lymphoid cells upon their initial exposure to antigen in the primary response. Cells which have thus been conditioned, but which morphologically are still indistinguishable from other lymphoid cells, react to a further dose of antigen by rapid transformation into blastoid cells. The blastogenic or mitogenic effect of tuberculin and other known antigens in previously sensitized individuals support these assumptions. This ability of immunologically competent cells to respond to antigen by transformation appears to be a general character of the immune response.[33,36] Here the antigen is clearly the stimulus which provokes antibody producing cells to proliferate. Although the etiology of sympathetic ophthalmia is still unknown, autoimmunization of one's own tissue, such as the uvea, may occur following a perforating ocular injury. Once sensitization is established, sympathetic ophthalmia develops. The results of the study lend support to the theory that lymphocyte sensitized to ocular tissues are present in patients with sympathetic ophthalmia. The suspected role of uveal sensitization in sympathetic ophthalmia is not new. Years ago, Woods and Friedenwald developed a skin test consisting of uveal pigment and found a significant correlation between positive skin reaction and the clinical occurrence of sympathetic ophthalmia.

Experimentally, homologous retinal and uveal sensitization with adjuvant has been repeatedly shown to result in clinically active uveitis in various laboratory animals.[37-46] However, there appear to be no major distinguishing pathologic differences between the diseases produced by these two immunizing tissues. Because of possible cross-contamination, due to the natural anatomic association of the disparate tissues, it is difficult at present to ascertain whether the disease-producing antigen(s) is the same. Von Sallmann[47] has shown in primates that chorioretinitis produced with homologous retina was unassociated with possible vascular and neural antigenicity, since control studies using heterologous kidney and homologous

choroid plexus as antigens failed to produce uveitis.

Unpublished experiments in our laboratory have shown that human uveal-retinal tissues contain at least six antigenic components. Because clear-cut anatomic separation of retina and uvea is difficult, if not impossible, only the combined uveal-retinal tissue extract was used in this experiment. Attempts to isolate the antigenic or transforming factor(s) through fractionation and purification are currently being carried out.

The enhanced lymphocytic response in patients with sympathetic ophthalmia is certainly modest compared to responses to other known antigenic stimulation. Depressed transformation is observed in active disease states, such as tuberculosis. Although antibody titers were not performed in our study, depressed transformation may be due to a specific antibody in the serum which reacts in vitro with the uveal antigenic determinants, thereby making them unavailable for antigenic stimulation of susceptible cells.

Although the present study demonstrates enhanced lymphocytic response to uveal antigen in sympathetic ophthalmia, it is still unclear whether the defect in this disease is primarily due to autosensitization. It is of interest to note that in the control group only the patient with Vogt-Koyanagi-Harada syndrome showed any significant degree of transformation. Pathologically, these two disorders are remarkably similar. But whether the enhanced in vitro blastogenic response to ocular antigens of these two conditions is in response to the same pathogenetic defect is not yet established.

It appears that the in vitro transformation phenomenon is a specific reaction between an antigen and sensitized cells. Because the normal reaction to antigenic stimulus is the production of antibody, it seems reasonable to suppose that the phenomenon of lymphocyte transformation is limited to antibody production.[3,4] The lymphocyte transformation in vitro is probably part of the delayed type of hypersensitivity reaction. It is noteworthy that in the graft-vs-host the response of the immunologically provoked small lymphocytes resembles that of tuberculin-stimulated cells under light and electron microscopic examination.[2,48,49]

PHA from the bean, Phaseolus vulgaris, has been shown to induce blastogenesis of lymphocytes when cultured with leukocytes of normal human peripheral blood.[50] Results of the present study indicate that the lymphocytes from all patients were markedly stimulated with PHA and the results of the two groups showed no significant difference in the percentage of cells transformed.

The exact manner in which PHA and other mitogens stimulate leukocytes to division is still not entirely clear. It appears that the mechanism requires PHA to attach itself onto a receptor structure in the leukocyte and thus initiate a biochemical reaction ultimately leading to cellular division. The mitotic property of various mitogens would thus be nonspecific. It is possible that antigen-stimulated cell division is brought about by a similar mechanism.[51] However, the low percentage of cell stimulation from ocular antigens in this experiment, compared to those obtained by PHA, implies that the mechanism may be different.

## Summary

Enhanced lymphocytic transformation was demonstrated in patients with sympathetic ophthalmia when their peripheral leukocytes were exposed to homologous uveal-retinal antigens in tissue cultures. Similar challenge failed to evoke any significant degree in blastogenesis in a control group of patients with active ocular disease other than sympathetic ophthalmia. The results indicate that in patients with clinically active sympathetic ophthalmia the lymphocytes were sensitized to some component or components of ocular tissues.

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# SYMPATHETIC OPHTHALMITIS

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Sympathetic ophthalmitis is generally considered to be a relentless ocular inflammation that leads to bilateral loss of vision in 60 to 70% of cases.[1] In fact, however, during a single course of therapy, the disease often remits, does not recur when therapy is discontinued,[2,3] and leaves no permanent visual loss in its wake.

Such a case of sympathetic ophthalmitis is reported here. This patient's non-traumatized eye responded to corticosteroid therapy and there was no permanent loss of vision. No evidence of recurrence was noted over a two-year period of follow-up observation.

## Case report

On April 28, 1969, a 37-year-old woman was seen with a blind, painful left eye following a penetrating injury one month earlier. The laceration had involved the cornea, sclera, and ciliary body and had been surgically repaired. Ocular examination of the right eye showed this eye to be normal with best corrected visual acuity of 20/25.

The blind left eye was soft to palpation. Examination revealed corneal stroma and epithelial edema with folds in Descemet's membrane. The anterior chamber was shallow and revealed marked cells and flare. A dense cataract was noted behind the eccentric and unreactive pupil. The retina was not visible. The eye was enucleated on April 29, 1969. Pathologic examination disclosed sympathetic ophthalmitis (Fig. 1).

On May 23, 1969, the patient complained of photophobia and decreased vision in her remaining eye. Best corrected visual acuity was 20/40 and a moderate number of cells and flare were noted in the anterior chamber. There were no keratic precipitates and the retina was normal.

She was treated with a corticosteroid (Prednisone) 80 mg daily, and the eye improved rapidly. Two weeks later, ocular examination was normal and visual acuity was correctible to 20/25. Corticosteroid therapy was gradually tapered; after six weeks of therapy it was discontinued. The patient experienced no further difficulty during the following 24 months.

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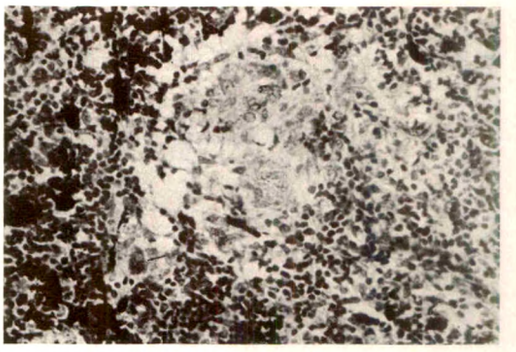


Fig. 1 (Brauninger and Polack). Granulomatous inflammation in the choroid. The epithelial cells contain numerous pigment granules (arrow) and a giant cell is present (hematoxylin-eosin, ×200).

## Pathology

Examination of the enucleated eye revealed a 9 mm laceration, surgically repaired, which had extended through the peripheral cornea and adjacent sclera, and involved the trabecular meshwork and ciliary body. The laceration was filled with fibroblastic tissue which was patchily infiltrated with small round cells. There was early neovascularization of the corneal stroma, with edema and infiltration of lymphocytes and polymorphonuclear leukocytes. In one quadrant the angle was obliterated by the iris root which was displaced forward against the cornea. The trabecular meshwork and iris root contained numerous scattered lymphocytes and plasma cells. Throughout the ciliary body and choroid there was a diffuse infiltrate of lymphocytes and scattering of eosinophils. Throughout the choroid there were nodular accumulations of epithelioid cells which contained fine pigment granules within their cytoplasm. These granulomatous foci of choroidal inflammation did not involve the adjacent choriocapillaris. The retina was totally detached and folded upon itself; however, the nuclear layers were well defined and without inflammatory involvement.

An organizing vitreous hemorrhage was present and the lens was cataractous but there were no inflammatory cells in or on the lens surface. Leukocytes and eosinophils were seen in the sclera along the ciliary nerves and emissary vessels.

## Discussion

Sympathetic ophthalmitis is characterized in its early stages by an insidious uveitis, anterior, posterior, or both, with disproportionate and early decrease in visual acuity in an eye that does not seem to be particularly red or painful.[2,4] Cells and flare in the anterior chamber are prerequisites for the clinical diagnosis, while keratic precipitates, swelling in the iris, papillitis or scattered yellowish spots in the fundus may occur early, all eventually leading to panuveitis.[2,4] The process in the "exciting" eye usually begins two weeks after injury and 80% of cases occur within three months.[1] The "sympathizing eye" becomes involved at the same time or shortly thereafter.

The incidence of sympathetic ophthalmitis has declined with modern surgical technique and postoperative care.[5] Nevertheless, the disease is a cause of great concern to the clinician who surgically repairs an injured eye and later finds both globes involved in an inflammatory process that threatens vision.

Sympathetic ophthalmitis may spontaneously remit without therapy, disappear under a course of systemic corticosteroids, or follow a complicated course characterized by remissions and exacerbations with eventual irreversible eye damage.[2-4] At present, prognosis is uncertain and not well understood, partly because those cases in which the course of the disease is mild are generally not reported in the literature. Further, the clinician who treats an apparent case of sympathetic ophthalmitis that responds quickly and completely is then inclined to doubt his own initial diagnosis, and pathologic confirmation is not usually available in mild cases. Nevertheless, Makley and Liebold[5] have indicated that a favorable visual result can be obtained with systemic corticosteroid therapy in 75% of cases.

The case of sympathetic ophthalmitis reported here emphasizes that this disease may present as a mild iritis which disappears during a course of corticosteroid therapy and does not recur or result in permanent clinical damage to the eye. Early detection of this disease process, combined with adequate corticosteroid therapy can provide a better visual result for the patient.[3]

## Summary

A pathologically documented case of sympathetic ophthalmitis in a 37-year-old woman began as a mild iritis which responded rapidly to systemic corticosteroid therapy and did not recur or result in permanent eye damage. This case is reported in support of the modern clinical impression that many cases of sympathetic ophthalmitis, with early recognition, adequate systemic corticosteroid therapy and careful patient follow-up, do not recur or cause permanent eye damage.

### Acknowledgment

We thank Ian C. Hood, M.D., for his study of this case, and R. W. Irwin for his photography.

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# EVULSION OF THE OPTIC NERVE

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The intraorbital portion of the optic nerve is relatively fixed to the optic foramen by its dural attachment. Optic nerve injuries caused by blunt trauma to the globe commonly occur at the foramen either by shearing of the motile portion of the nerve or by hemorrhage and edema within the confined sheath spaces. Since the anterior portion of the nerve is motile, it is uncommon to incur injury at the papilla. It is our purpose to present a rare case of evulsion of the optic nerve.

## CASE REPORT

A 29-year-old man claimed complete loss of vision in his left eye immediately after being "jabbed" with a finger while playing basketball. Concurrently he experienced a transient intense flash of light in that same eye. He was seen at the Cook County Hospital one hour after the accident, at which time he complained of severe left frontal headache and nausea.

Ocular examination revealed vision in the right eye to be 20/20 without correction. There was no light perception in the left eye. The anterior and posterior segments of the right eye were normal. Applanation tensions were within normal limits in both eyes. There was no external evidence of trauma or enophthalmos in either eye and the ocular motility was full.

Biomicroscopic examination showed the pupil of the left eye to be in mid-dilatation. It did not react directly to light, but responded consensually. A few scattered cells were seen in the anterior chamber of the left eye. The lens appeared to be clear and in its normal position. There was gross hemorrhage in the posterior nasal vitreous, fanning out from the disk. The margin of the left disk was skirted with a "sunflower" hemorrhage of moderate extent (Fig. 1). The central retinal vessels were displaced nasally and superiorly. An elliptical excavated defect was noted in the inferior quadrant of the disk. No posterior limit was discernible. There was no evidence of vitreous filling the defect. It appeared that clear serous fluid occupied the excavated cavern in the disk.

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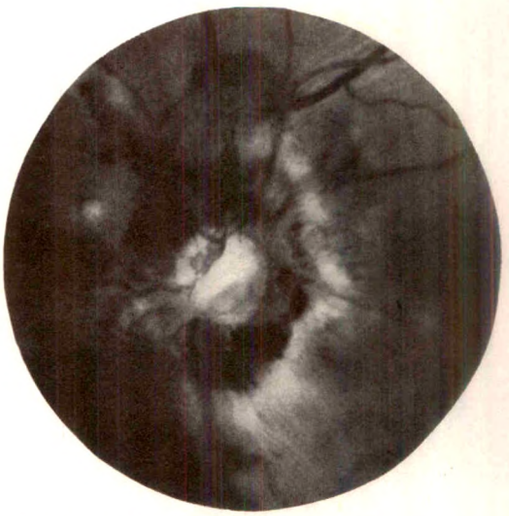


Fig. 1 (Park, Frenkel, Dobbie, and Choromokos). Excavated defect of the optic nerve and vitreoretinal hemorrhage at admission.

Moderate retinal edema was noted in the paramacular as well as papillomacular area. Retinal folds radiated from the temporal margin of the disk toward the macula.

The retinal vessels appeared to be normal in caliber and color. The peripheral retina was unremarkable. Fluorescein angiography substantiated this finding. At 29 seconds following the dye injection, the blood vessels were full and clearly outlined (Fig. 2).

Four weeks after the initial trauma, gliosis was apparent, filling the defect in the disk (Fig. 3). At six weeks further gliosis of the optic nerve and peripapillary areas was evident. The vitreous and retinal hemorrhages were essentially resorbed (Fig. 4).

At three months the depression of the optic nerve head was completely filled by fibrotic tissue. A white veil of tissue protruded into the vitreous from the inferonasal margin of the disk (Fig. 5).

## DISCUSSION

An unusual instance of evulsion of the optic nerve head has been documented by serial photography and fluorescein angiography.

The mechanism of optic nerve evulsion has been elaborated by various authors. Salzmann[1] defined evulsion of the optic



Fig. 2 (Park, Frenkel, Dobbie, and Choromokos). Fluorescein angiography during the venous phase demonstrating full and normal blood vessels and preretinal hemorrhage obscuring choroidal pattern in the peripapillary area five days following trauma.

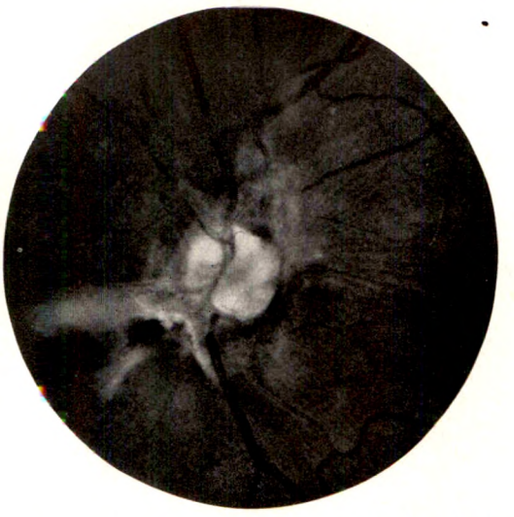


Fig. 4 (Park, Frenkel, Dobbie, and Choromokos). Six weeks after trauma, further gliosis and clearing of vitreous and retinal hemorrhage are evident.

nerve as the forceful backward dislocation of the optic nerve from the scleral canal without any break in the continuity of the adjacent coats of the globe.

While most cases have massive intraocular hemorrhage and disorganization, the present case is unique and interesting in that no evidence of external ocular injury was seen, even though the patient sustained evulsion of the optic nerve by the forceful jab of a finger into his orbit.

Among the various explanations of the mechanism of evulsion of the optic nerve, the most universally accepted theory impli-

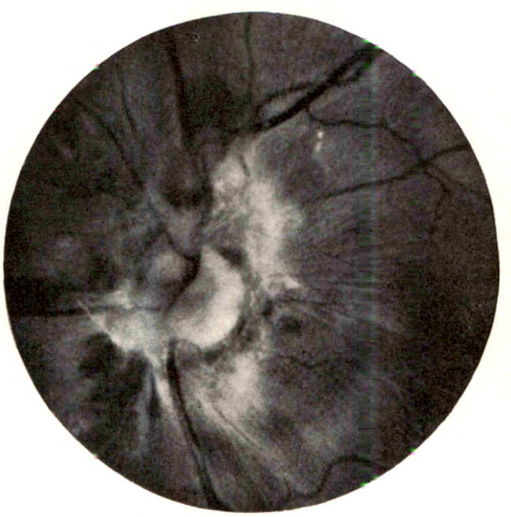


Fig. 3 (Park, Frenkel, Dobbie, and Choromokos). At four weeks following trauma, gliosis fills the defect in the disk and retinal folds radiate toward the macula.



Fig. 5 (Park, Frenkel, Dobbie, and Choromokos). At three months, complete gliosis of the excavated cavern of the optic nerve has occurred; a veil of fibrotic tissue protrudes into the vitreous.

cates extreme rotation and forward dislocation of the globe. A tear of the lamina cribrosa results, this being the weakest portion of the ocular envelope.[2] Simultaneously, the nerve fibers are torn at the margin of the disk. At this level, they consist merely of naked axon cylinders without supporting myelin sheath and may retract a variable distance up the sheath once they are torn.[3] The sheath, being elastic, can stretch and retain its continuity. This mechanism may apply to our case.

Lister[3] proposed that a blow on the front of the eye produces a sudden increase in intraocular pressure, rupturing the lamina cribrosa and expelling the nerve. He stated that such cases would be correctly described as expulsion rather than evulsion of the nerve.

In another vein, Lagrange[4] theorized that an indirect facial injury sets up concussion waves which travel through the pterygomaxillary fissure into the orbit. The globe is then propelled forward, stretching the nerve and causing evulsion.

Direct injury to the intraorbital portion of the optic nerve in cases of gunshot or knife wounds can result in the evulsion of the optic nerve by retropulsion.

Because of similarities in appearance, coloboma of the disk must be considered in the evaluation of evulsion of the optic nerve.[5] In this static condition one does not find retinal and vitreous hemorrhages nor subsequent gliosis which are always seen with evulsion of the optic nerve.

Congenital pit of the optic nerve head is sometimes associated with serous detachment of the macula. Fluorescein angiography may demonstrate a focal decrease in vascularity in the region of the optic pit or leakage of dye from the capillaries around the pit.[6] Fluorescein angiography performed in our patient failed to demonstrate any of these features of congenital optic nerve pit.

Pathologic examination of cases of optic nerve evulsion demonstrates a fairly constant site of injury. The rupture of the nerve is found at the level of the termination of Bruch's elastic lamina. The fibers of the lamina cribrosa are torn and the nerve retracts.[3]

Although the evulsion of the optic nerve head in our case involved only the inferior temporal quadrant of the left disk, there was no light perception in the eye. Kommerell[7] reported a case of partial evulsion of the optic nerve where his patient retained a visual acuity of 20/400 and demonstrated a visual field defect commensurate with the extent of the optic nerve evulsion.

## Summary

An unusual case of evulsion of the optic nerve without visible evidence of external ocular trauma was observed by serial fundus photography. Fluorescein angiography was normal. Extreme rotation and forward dislocation of the globe causing tear of nerve fibers at the lamina cribrosa with subsequent retraction along the nerve sheath are implicated.

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# MODIFIED CEILING-MOUNTED ZOOM OPERATING MICROSCOPE

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Various methods of mounting an operating microscope on the ceiling have been developed by Barraquer, Draeger and others.[1-7]

The ceiling mounting eliminates the awkwardness and inconvenience caused by a supporting table or floor column. In order to utilize Barraquer's method, however, the operating room must be specifically designed to accommodate the microscope, while Draeger's method involves considerable expense, with too many things attached to the microscope. We have developed a less expensive and more efficient method of ceiling mounting by making a number of modifications in the Zeiss zoom microscope (OPMi-II) and a Zeiss foot plate. The modified foot plate permits remote control of the microscope.

## MATERIAL AND METHOD USED FOR CEILING MOUNTING

The microscope was disconnected from its stand and fixed to the ceiling column of a Siemens 3-D overhead support used for x-ray tubes, using an intermediate plate (Fig. 1). All electrical parts were removed from the foot-casing of the Zeiss stand and built into the ceiling column of the Siemens. Cables were used to connect the ceiling column to a foot plate which was provided with all essential control switches. The coarse-gross positioning along the vertical axis, with a range of 165 cm, and a speed of 40 cm/second, is changed by the Siemens column. Fine focusing, with a speed of 5 mm/second, is altered within the operating microscope itself. When the microscope is retracted, it is 272 cm from the floor, with this suspension method thus allowing the surgeon to make the fullest use of the operating lamp (Fig. 2).

*Fitting the microscope to the ceiling column*—A shorter working distance between the surgeon and the operating field was attained by replacing the inclined tube of 160 mm with one of 125 mm, and the objective of 200 with 150. The coaxial illuminator was removed and two fiber bundle illuminators,* with condenser lenses attached to their ends, were installed on the circumference of the 150 mm objective. The working distance was thus shortened from 475 to 365 mm. In theory it should be 300 mm, but the surgeon still can work in a relaxed posture when the

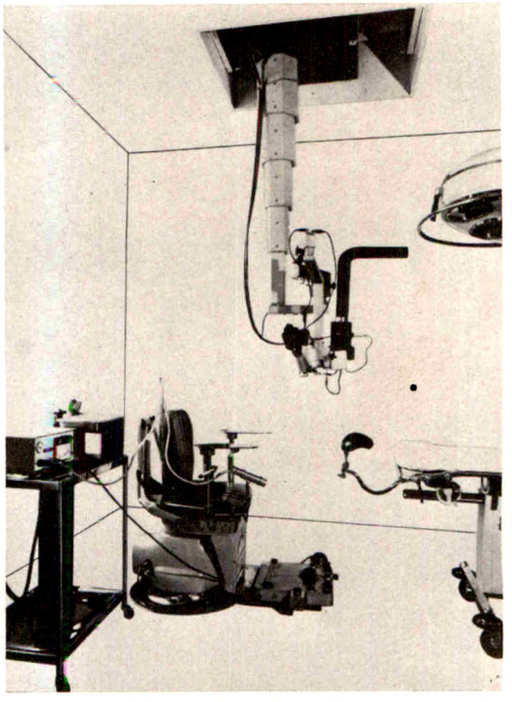


Fig. 1 (Sugita and Sugita). The operating microscope, the operating stretcher-table, the operating chair and the operating lamp shown in their relationship to one another. With the exception of the operating table, all are remotely controlled by the foot switches. Thus, the surgeon can maneuver the operating lamp without changing his position. On the right side of the chair is the casing for the Amoils cryopencil.

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* The fiber optics bundles were made by the Nagashima Medical Company, Tokyo, Japan.

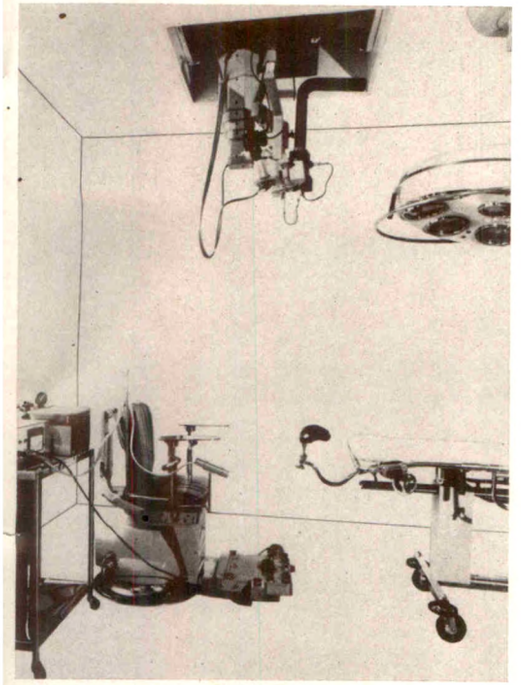


Fig. 2 (Sugita and Sugita). Same view as shown in Figure 1, but with ceiling mounted microscope in fully retracted position.

distance is 365 mm. The clearance between the objective lens and the patient's eye was reduced to 140 mm by the addition of the condenser lenses. However, this distance proved sufficient to allow both the surgeon and the assistant to work together satisfactorily. Furthermore, the use of the two fiber bundle illuminators eliminated disturbing shadows cast by the surgeon's hands when additional oblique illuminators are employed. Since the light intensity was increased by approximately 100%, additional flash is no longer necessary for photography.

*Modification of the foot plate*—Button switches were added to the Zeiss foot plate for the positioning of the microscope, the zoom, the operating lamp, and the chair, and for photography.

## Modification of operating chair

In microsurgery it is essential that proper focus on the operating field is maintained at every step of a surgical procedure. It is equally important that the surgeon's hands remain free so that he may concentrate their effort on the surgical maneuver. It follows that the adjustment of focus may be best performed with foot controls if the surgeon is seated in an operating chair.

One of the most important considerations in regard to the operating chair, however, is whether the surgeon should remain in a fixed position or be able to move around the patient's head. Dannheim developed a chair that allows the surgeon to move around the patient's head while remaining seated, but after some experience with this device, he revised his opinion and stated that a static and relaxed position is better. Barraquer[8] and others concur with the latter opinion.

For practical purposes it is advisable that the operating chair be provided with arm rests. These may be designed to support the surgeon's arms at the elbows, at the forearms, or near the wrists. Mackensen[9] pointed out the arms would be most secure if they are supported near the wrists, but this would prove somewhat inconvenient in cases where considerable movement of the forearms is required (for example, corneal incision with a cataract knife). If the only support is at the elbows, on the other hand, the elbows may tend to slide. These considerations led us to develop a fixed-position chair that can be moved up and down smoothly by foot controls (upward, 40 mm/second; downward, 8 mm/second) in order to obtain different levels of support from the screw-fixed arm rests for different steps of the various surgical procedures. In suturing, for example, the arm rests should be 30 mm below the level of the patient's eye, but for making a corneal incision the arm rests should be lowered 70 mm. For further convenience, the arm rests are designed to rotate horizontally on the axis of a supporting column. By the use of a spring device, the arm rests can be turned to any desired angle. Finally, if the surgeon must leave the chair during the operation, the arm rests can be pushed outward. On the right side of the

chair there is a support for the Amoils cryopencil hose and a casing for insertion of the pencil when it is not in use. Operating maneuvers are further facilitated when this operating chair is used in combination with an operating table supplied with an adjustable headrest. The spatial relationship between the surgeon's eyes, his hands, and the operating field can thus be made the same for every patient. In certain special operations (goniotomy, etc.), the desired angle of approach may be obtained by rotating the chair and placing the operating table diagonally toward either side.

## Summary

The 3-D overhead tube support for x-ray tubes (Siemens) was used for the ceiling mounting of the Zeiss zoom (OPMi II) operating microscope. The facilities of the microscope were further increased by replacement of the coaxial illuminator with two fiber optic bundles for increased illumination without shadowing. In addition, a relaxed posture was achieved for the surgeon by the development of a fixed, but adjustable operating chair provided with a foot plate for the remote control of the microscope and the chair.

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# PERIPHERAL RETINAL NEOVASCULARIZATION IN CHRONIC MYELOCYTIC LEUKEMIA

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Leukemic retinopathy is common in both acute and chronic myelocytic and lymphocytic leukemia at some stage in the course of the disease. Clinically and histopathologically, infiltration of the conjunctiva, episclera, sclera, choroid, iris, ciliary body, optic nerve, retina and rarely the vitreous may be seen. There may be hemorrhage involving the conjunctiva, episclera, anterior and posterior chambers, retina, choroid and vitreous. Focal necrosis of the retina involving the nerve fiber layer and ganglion cell layer have been described as well as serous retinal detachment.

Retinal vessel and choroidal background color changes which reflect an increased leukocytosis or decreased erythrocyte concentration have been reported. In addition, there have been reports of vascular dilatation, irregularity in vessel caliber, tortuosity of the veins and to a lesser extent the arterioles, grey-white linear sheathing of vessels, hard yellow-white exudates, microaneurysms, and soft cotton-wool patches. Flame shaped, rounded, deep or preretinal hemorrhages and subretinal hemorrhages also have been noted. They often have a white central component which may appear, singly or multiply, even when hemorrhages are absent.[1-9]

This paper describes a case of peripheral retinal neovascularization in a patient with chronic myelocytic leukemia which may be unique in the ophthalmic literature.

## CASE REPORT

A 32-year-old black man was first seen in the hematology clinic at the Hospital of the University of Pennsylvania, July 7, 1969, with a three-month history of anorexia, 25-pound weight loss, fatigue, weakness, upper abdominal discomfort, and pains and knots in the legs. One month prior to examination he had noted muscle pain and pruritis of both legs. He had observed painless swellings, 2 to 3 cm in diameter, which spontaneously disappeared in three to seven days, on his left side, both thighs and ankles. The past medical history and family history were noncontributory.

Physical examination revealed a well-developed, somewhat thin man in no acute distress. Blood pressure was 110/85 mm Hg, pulse 80 and regular, respirations 16 per minute, and temperature 37°C orally. Small hemorrhages were noted in both fundi. There was slight enlargement of the cervical lymph nodes and moderate general lymphadenopathy. Heart and lungs were within normal limits. The liver was not palpable, but the spleen was firm and greatly enlarged.

Laboratory values revealed a hemoglobin of 9.5 g%, white blood count of 340,500 $mm^3$, hematocrit 44%, reticulocytes 3.2% and platelets 328,000 $mm^3$. Differential smear contained 41 polymorphonuclear leukocytes, 10 band forms, three eosinophils, one basophil, four monocytes, two lymphocytes, 27 myelocytes, eight metamyelocytes, and four promyelocytes. There was 2+ hypochromasia and polychromasia. Hemoglobin electrophoresis had 96.5% type A and 2.6% type $A_2$ hemoglobin; protein electrophoresis showed only a slight elevation in the gamma fraction of 1.52 g%, the normal range being 0.62 to 1.2 g%. Fasting blood sugar was 60 mg%, Sia test was negative, and immunoelectrophoresis, serum viscosity studies, and test for cryoglobulins were unremarkable. Bone marrow aspirate showed many early myelocytic forms with a high myeloid:erythroid ratio. Chest x-ray examination was within normal limits. The patient was treated with busulfan (Myleran) 8 mg and allopurinol (Zyloprim) 300 mg daily.

Follow-up examination, July 14, 1969, showed the white blood count elevated to 524,500 $mm^3$, and the medication was continued. On August 4, 1969, the patient had improved subjectively with a return of appetite and strength. The spleen was no longer palpable, and the leukocyte count had dropped to 45,000 $mm^3$. By November 3, 1969, the white count had dropped to 9150 $mm^3$ after a course of busulfan therapy.

Subsequently, with regulation of busulfan and chlorambucil (Leukeran) treatment the blood leukocyte count ranged between 8700 and 97,300 $mm^3$, averaging 40,000 $mm^3$, with the maintenance of subjective well being on the part of the patient.

On February 22, 1971, an eye consultation was obtained because of follicular conjunctivitis in both eyes and a small chalazion of the left lower

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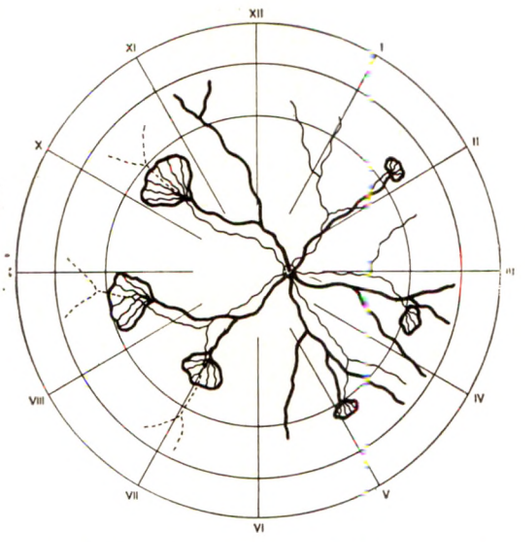



Fig. 1 (Morse and McCready). Right eye. Fundus diagram showing sea fan neovascularization. The obliterated terminal arterioles are represented as broken lines, veins as thick lines and arteries as thin lines.

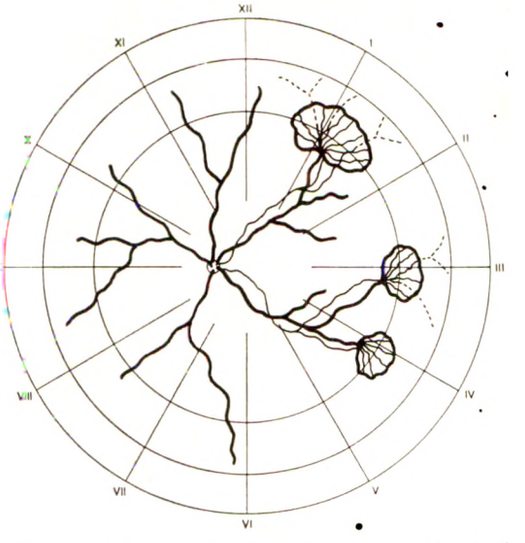



Fig. 2 (Morse and McCready). Left eye. Fundus diagram showing the areas of neovascularization. The obliterated terminal arterioles are represented as broken lines, veins as thick lines and arteries as thin lines.

eyelid. The patient had never worn spectacles and had never been troubled with impaired vision. There was no family history of ocular disease. Visual acuity without corection was 6/6-1 and Jaeger 1 for near in both eyes. With the exception of the conjunctivitis and the small chalazion, external and slit lamp examinations were within normal limits. The intraocular pressure was 7.5/5.5 = 11.2 mm Hg (Schiøtz) in each eye. Ophthalmoscopy revealed clear media with normal disks and maculae in both eyes. There was slight fullness of the veins and small- to medium-sized blot and preretinal hemorrhages, some with white centers, in each eye. A few small microaneurysms were seen. Peripheral linear white sheathing of some arterioles and veins was noted as well as white with and without pressure. Large and small areas of neovascularization with a sea-fan configuration and gliosis were observed at the equator and just posterior to the equator in both eyes. The average size of these neovascular areas was two to three disk diameters. The right eye had six such sea-fans at 2, 3:30, 4:30, 7, 8:30 and 10:30 o'clock (Fig. 1). The left eye had three areas of neovascularization, the largest at 1:30 o'clock, covering a four- to five-disk diameter span, with smaller ones at three and four o'clock (Fig. 2). Anterior or further peripheral to these patches of new blood vessel formation the terminal branch arterioles appeared white and seemingly obliterated (Figs. 3–5). Fundus fluorescein angiography confirmed the branch arteriolar obliteration and showed late-stage neovascular leakage (Figs. 6 and 7).

## Discussion

Clinically, it is not possible to separate the various leukemias and related diseases on the basis of ocular findings alone. The retinal changes seem to appear without any definite

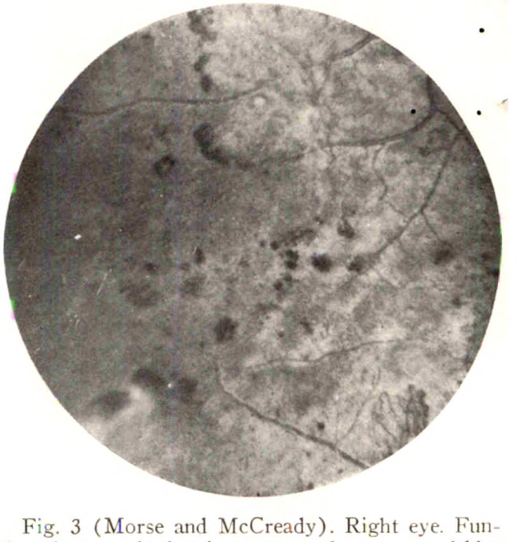


Fig. 3 (Morse and McCready). Right eye. Fundus photograph showing neovascular areas and blot hemorrhages.



Fig. 4 (Morse and McCready). Right eye. Fundus photograph showing a single neovascular patch with blot hemorrhages.

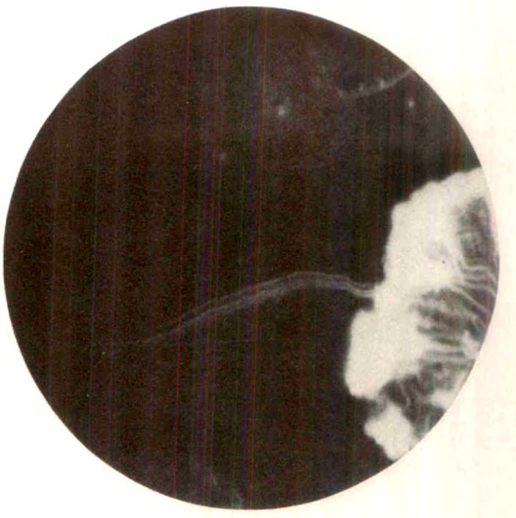


Fig. 6 (Morse and McCready). Right eye. Early arteriolar phase fluorescein angiogram showing neovascular sea fan with peripheral rim of hemorrhage appearing darker.

relation to the degree of anemia, thrombocytosis, or leukocytosis, and may disappear during the treatment of leukemia.[9] In one pathologic study, the finding of microaneurysms was confined to those patients who had died of chronic lymphocytic and myelocytic leukemia.[7] Similar, if not identical fundus changes are described in macroglobulinemia, multiple myeloma, cryoglobulinemia, lymphomas, paraproteinemias, and dysproteinemias.[10] One must also consider diabetes

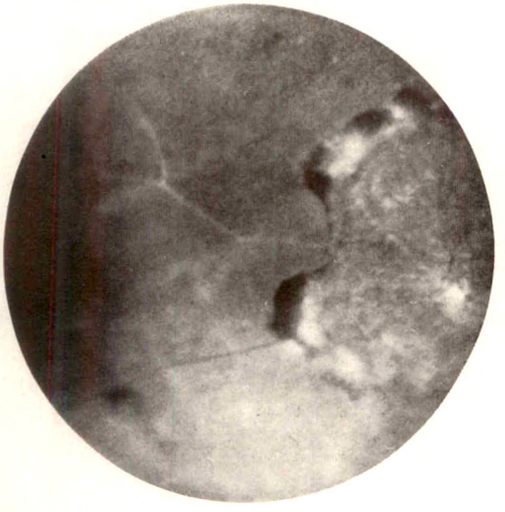


Fig. 5 (Morse and McCready). Right eye. Fundus photograph showing larger sea-fan shaped area of neovascularization with some hemorrhage localized to the peripheral rim. A white obliterated branch arteriole is seen more peripherally.

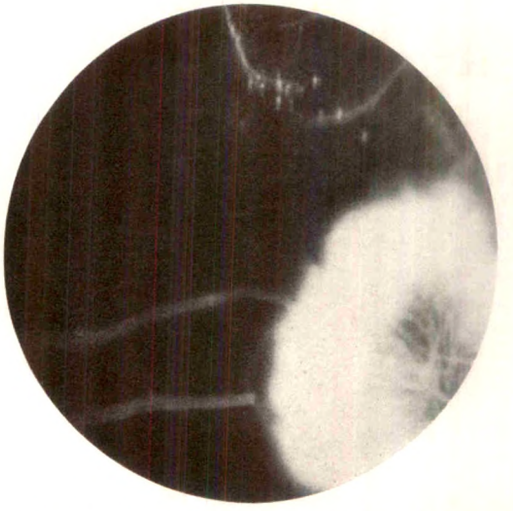


Fig. 7 (Morse and McCready). Right eye. Arterio-venous phase fluorescein angiogram showing vein and main arteriole to be patent and confirmed arteriolar branch occlusion.

mellitus, sickle cell hemoglobinopathy, Eales' disease, polycythemia, central retinal vein occlusion, carotid cavernous sinus fistula, and congenital tortuosity and dilatation of the retinal vessels.

Hyperviscosity of the blood may be due to increased cellular content or serum factors. A previous examination of patients with serum hyperviscosity, in cases of cryoglobulinemia and hypergammaglobulinemia, found histopathologic evidence of attempted new vessel formation in the form of microscopic endothelial nests.[11]

Neovascularization of the type here reported has not been previously described in leukemia. The extensive neovascularization with sea-fan morphology in the reported case is strikingly reminiscent of that seen in the sickle cell hemoglobinopathies.[12] Further studies of this retinopathy, seen most commonly with S-C hemoglobins, and more rarely in S-thalassemia, S-S and S-A, have shown it to be a response to vaso-obliteration preceded by arteriolar occlusion, peripheral arteriovenous anastomosis, with neovascular and fibrous proliferation which may lead to vitreous hemorrhage and retinal detachment.[13]

Examinations have shown a significant increased blood viscosity with a white blood cell count over 50,000 mm³ above which level the blood viscosity increases directly in relation to the number of circulating white cells.[14]

The presumed mechanism for this case of leukemic neovascular retinopathy involves the increased blood viscosity caused by the markedly elevated number of circulating white blood cells, resulting in obliteration of the terminal arterioles and thereby provoking the neovascular response. The findings in the reported case of leukocyte counts of 340,500 and 524,500 mm³ early in the course of the patient's examination and treatment, the absence of alteration of the serum viscosity, as well as the absence of coexisting paraproteinemia or dysproteinemia, and the finding of obliterated arterioles peripheral to the neovascular areas are all consistent with this hypothesis.

## Summary

A 32-year-old man with no visual complaint and chronic myelocytic leukemia was examined 19 months after diagnosis. Ophthalmoscopy revealed large and small areas of neovascularization with a sea-fan configuration and gliosis at the equator and just posterior to it in both eyes. Increased blood viscosity caused by a markedly elevated number of circulating white blood cells that obliterated the terminal arterioles and thereby provoked a neovascular response are presumed to be the mechanism for this case of leukemic neovascular retinopathy.

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# RETINAL CHANGES IN CONGENITAL POIKILODERMA

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In 1923, Thomson[1] reported two infant sisters who had a bright red, tense swelling of the face and body. Through this swelling there gradually appeared a telangiectatic network which subsided after the passage of several months, leaving a linear reticulated pigmentation. These changes were very similar to those described by Rothmund[2] in 1868, and later by Wodniansky[3] in 1957. Abnormalities which occur in congenital poikiloderma affect the skin predominantly and consist of telangiectasia, atrophy, and pigmentation which may be smudged or reticulated. The onset of the skin changes is generally in infancy, usually between the third and sixth month of life. Reviews of the literature and case reports[4-8] have emphasized that girls are more often affected and that there is a familial history in about 70% of cases. The primary ocular manifestations are cataracts, and these are present in 52% of cases. The present report is of interest because it is a case of congenital poikiloderma with retinal changes.

## CASE REPORT

A six-year-old white girl was seen for a routine eye examination. There were no ocular symptoms and the only antecedent history was the dermatologic diagnosis of congenital poikiloderma established during the first year of life. There was no familial history of the disease and no systemic abnormalities were present. The skin changes consisted of diffuse telangiectases over the entire body. These were particularly prevalent on the face (Fig. 1). Visual acuity was RE: 20/20, LE: 20/20. Pupillary reactions, motility, and slit-lamp examination of the anterior segment were all normal. Ophthalmoscopy with scleral depression revealed a normal fundus in the right eye, but in the left eye peripheral aneurysmal dilations of the retinal veins were noted just anterior to the equator (Fig. 2). No exudation was present in the fundus. Periodic retinal examinations have been continued and over the last two years, no change has taken place, and the patient has remained asymptomatic.



Fig. 1 (Tasman). Telangiectasia of skin in patient with congenital poikiloderma.

## DISCUSSION

This case is of interest because it describes retinal changes in a patient with presumed congenital poikiloderma. The primary features were capillary telangiectatic changes in the skin. No abnormalities of the skeleton, loss of hair, defects of the nails and

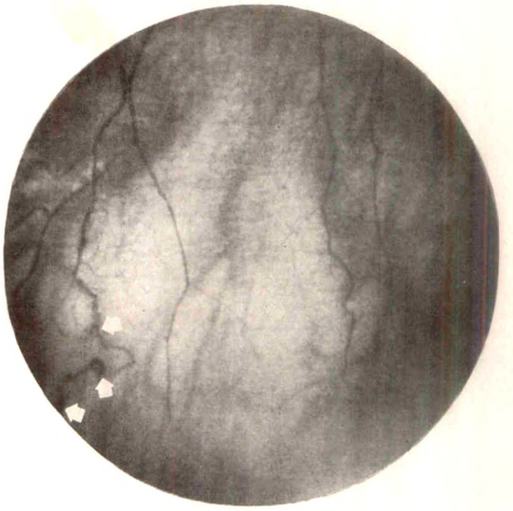


Fig. 2 (Tasman). Aneurysmal vascular changes (arrows) in a patient with congenital poikiloderma. The change is similar to that sometimes seen in Coats' disease.

This study was supported by the Retina Research and Development Foundation, Philadelphia, Pennsylvania.

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teeth, disturbance in sexual development, saddle-nose or syndactylism were noted, and no hereditary history could be elicited. Thus, it is difficult to comfortably categorize this patient as having Rothmund's, Thomson's or Wodniansky's syndrome, xeroderma pigmentosum, dyskeratosis congenita, anhidrotic ectodermal dysplasia, Werner's syndrome, or progeria, all of which may have overlapping characteristics.

In the past, cataract is the ocular complication emphasized in many of these syndromes. These were absent at the time of examination, but peripheral aneurysmal dilations of the retinal veins were present in one eye and were similar in appearance to those sometimes seen in Coats' disease. No exudation was present at the initial examination and none has developed over the two years during which the patient has been followed.

## Summary

Peripheral aneurysmal dilations of the retinal vein were noted anterior to the equator in the routine examination of a six-year-old white girl with congenital poikiloderma. She had diffuse telangiectases over the entire body, but was otherwise without symptoms or complaints. In the past, the main complication of this disease was thought to be cataracts. Cataracts were absent in this patient, but retinal vascular changes were present similar to those sometimes seen in Coats' disease. The patient's eyes were asymptomatic, however, and there was no subretinal exudation at the time of her initial examination nor during the two years in which she was followed.

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# INTRACRANIAL HYPERTENSION AND TETRACYCLINE THERAPY

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Intracranial hypertension secondary to tetracycline therapy in infants is frequently recorded.[1-4] The occurrence of this syndrome in adults is apparently rare, with only one patient thus far reported.[5]

This paper presents an additional case; in an adolescent girl with acne, papilledema was associated with the oral administration of tetracycline.

## CASE REPORT

A 16-year-old white girl was admitted to Sinai Hospital of Detroit with a five-day history of severe headaches, dizziness, nausea, and occasional vomiting. The patient stated that she was feeling entirely well prior to the present illness. Tetracycline therapy in a dosage of 250-500 mg daily had been employed in the preceding five months for treatment of acne.

Physical examination at admission revealed evidence of bilateral papilledema with scattered superficial hemorrhages and a few exudates around the disks bilaterally. Except for blind spot enlargement, visual fields were normal. The remainder of the general physical and neurologic examination was entirely within normal limits, except for the complaint of low back pain with extreme flexion of the neck. There was no evidence of nuchal rigidity.

Routine laboratory examinations, including complete blood counts, urinalysis, sedimentation rate, and 24-hour urine studies for 17-keto- and 17-hydroxy-corticosteroids, were within normal limits. Antistreptolysin-O titer, infectious mononucleosis tests were normal; and estimations of blood urea nitrogen, serum calcium, serum phosphorus, and serum electrolytes were also normal. VDRL was nonreactive. The patient was seen in consultation by a neurosurgeon, and neurologic studies including brain scan, electroencephalography, arteriography, and pneumoencephalography; these were reported as being within normal limits. Skull and chest x-ray studies were also normal. Cerebrospinal fluid obtained at the time of the pneumoencephalogram showed no cells protein 16 mg%, and negative cultures. Cerebrospinal fluid pressures were not recorded by the neurosurgeon who performed the spinal tap in the upright position during pneumoencephalography.

The patient brought her tetracycline with her to the hospital, and for several days after admission she continued to take this medication. When this was discovered, the medication was discontinued. Following discontinuance of the tetracycline, the patient noticed a definite improvement in the severity and frequency of her headaches until the time of pneumoencephalography, when severe frontal headaches began to occur. These headaches seemed typically postspinal in nature, with relative comfort in the supine position and exacerbation of the pain upon sitting or standing up. Over a two-week period, the papilledema gradually regressed and the optic disk margins were once more sharp, with resolution of the previously noted hemorrhages and exudates. The headaches persisted, however, despite prolonged bedrest and a trial course of intravenous lactated Ringer's solution. It was felt that the patient would best benefit by convalescing from the postspinal headaches at home. Accordingly, she was transported by ambulance in the supine position to her home.

Shortly thereafter, the headaches disappeared. On follow-up examination six weeks later, central visual fields were normal to a 2 mm white test object at 1000 mm. Vision was 20/20 in each eye, and the optic nerves were normal bilaterally.

## DISCUSSION

This case calls attention to the association between intracranial hypertension and oral tetracycline therapy. The disease states known to produce papilledema and increased intracranial hypertension are noted by Buchheit, Burton, Haag, and Shaw.[6] In addition to tetracycline therapy, nalidixic acid,[7] excess or deficiency of vitamin A,[8] and prolonged corticosteroid administration[1] are implicated as possible etiologic factors in the production of intracranial hypertension. Before a consideration of these agents as possibly causing this patient's intracranial hypertension, space occupying lesions—brain tumors, abscess, or hematoma—and hypertensive encephalopathy were eliminated by careful history, physical examinations, and pneumoencephalography. Medical causes such as hypocalcemia (secondary to hypoparathyroidism), Addison's disease, and pulmonary emphysema were also ruled out by appropriate x-ray and laboratory studies.

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The possibility of associated hematologic disorders—sickle cell disease, macroglobulinemia, and polycythemia—was also eliminated as unlikely, and hemoglobin electrophoresis, or immuno-electrophoresis studies were not performed. Since the patient was a Caucasian, sickle cell disease was considered improbable; polycythemia was ruled out following normal peripheral blood counts; and the prompt spontaneous reversal of the central nervous system process belied the presence of macroglobulinemia.

The absence of prior signs and symptoms related to the menses was considered sufficient evidence to eliminate this entity as contributing to the patient's increased intracranial pressure.

Tetracyclines are now commonly employed in the therapy of acne vulgaris, thus a large number of patients are presently being exposed to these agents. In view of the infrequency of the association of intracranial hypertension with the administration of tetracycline in this large patient population of young adults, one might question whether the association in this patient was coincidental. Prompt response to the withdrawal of this agent, coupled with the previously well-described syndrome in infants, argues against this.

Buchheit and associates[6] suggest that the terms commonly used to describe this entity —"benign" intracranial hypertension or pseudotumor cerebri—should be eliminated since the syndrome is neither uniformly benign nor a false tumor. They proposed two designations more apropos: when the etiology is known, the syndrome should be described as intracranial hypertension secondary to the known factor (tetracyclines, for example); where no cause for the process is isolated, it should be designated as idiopathic intracranial hypertension.

## Summary

Intracranial hypertension probably secondary to tetracycline therapy was seen in a 16-year-old girl. Definite improvement occurred following cessation of tetracycline therapy. Laboratory examinations ruled out the commonly associated disease states associated with the production of papilledema and increased intracranial pressure. The terms intracranial hypertension associated with a known etiology (in this case, tetracycline), or idiopathic intracranial hypertension (when no cause is found) are suggested in place of the commonly used terms "benign" intracranial hypertension or pseudotumor cerebri to describe this disorder.

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# MODIFIED LANDOLT RINGS AND SLOAN LETTERS IN ADULT VISUAL ACUITY SCREENING

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A major problem involved in the development of a visual acuity screening program for adults is the selection of test targets which have been adequately standardized with those in common use. The broken ring of Landolt was introduced in 1889[1,2] and adopted as the standard test object by the Eleventh International Ophthalmological Congress in Naples in 1909.[3] The Committee on Optics and Visual Physiology of the American Medical Association recognized the problem of standardization in 1930 when they demanded that all test letters for visual acuity be based on comparison with the standard test—the Landolt ring.[4] Aware that the Snellen letters were not of equal difficulty in recognition, in 1951 Sloan[5] proposed the choice of 10 familiar sans serif letters of nearly equal legibility. In 1952, Sloan, Rowland and Altman[6] presented 10 such letters that had vertical, horizontal, and oblique contours. This assured that blurring in any one axis would impair recognition of the letter. The Snellen principle was adhered to in their design in that the height and width of the letters was five times the width of the strokes. Sloan and her associates showed that the Sloan letters yielded scores which were comparable to those achieved with Landolt rings. This study was done with a vision testing device which simulated the optical distance by means of a system of lenses.

Those involved in the development of vision screening programs assumed that testing with Landolt rings or Sloan letters would yield approximately equal numbers of "abnormals." This paper reports the significant difference in scores and numbers of "abnormals" generated by testing with commercially available Sloan letter and modified Landolt ring slides in a vision testing device. The testing of monocular vision with the modified Landolt rings under conditions of binocular seeing is also reported.

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## MATERIALS AND METHODS

Among the patients who appeared for routine multiphasic health testing at the Baltimore Public Health Service Hospital two groups were formed, each consisting of 100 patients, and all were tested on a Titmus (T/O) Vision Tester. This is a stereoscopic instrument that tests far vision at an optical distance of 20 feet through the interposition of lenses. Near vision is tested at 14 inches without the interposition of lenses. Far vision is tested at 15 degrees below the horizontal plane, and near vision at approximately 45 degrees below the horizontal. The targets are reproduced on slides. Patients who wore corrective lenses for near and far vision were allowed to wear them for that particular test. All testing was done by paramedical personnel skilled in health evaluation testing.

Both groups were tested with the modified Landolt ring slides, and with the Sloan letter slides. Tests were administered in the following order: Landolt-far, Sloan-far, Landolt-near, Sloan-near. Right eye was tested before left in each case. The modified Landolt ring slide contains a group of diamond-shaped borders each containing four rings. Three of the rings have a break in an oblique axes. The patient is asked to name the position of the ring without the break. The examination on the modified Landolt rings continues until the patient misses two consecutive answers. The maximum allowable number of errors per visual acuity level on the Sloan letter slides is dependent on the number of letters at that level (Table 1).

TABLE 1

SLOAN LETTER CHARTS

| Acuity Level | | No. Letters | No. Errors Allowed |
|---|---|---|---|
| Far | Near | | |
| 20/200 | 14/140 | 1 | 0 |
| 20/100 | 14/70 | 2 | 0 |
| 20/70 | 14/49 | 4 | 1 |
| 20/50 | 14/35 | 5 | 1 |
| 20/40 | 14/28 | 6 | 2 |
| 20/30 | 14/21 | 7 | 2 |
| 20/25 | 14/17.5 | 7 | 2 |
| 20/20 | 14/14 | 8 | 3 |

Both the modified Landolt ring and Sloan letter slides have different targets for far and near, as well as left and right eye. There are 10 acuity levels for the modified Landolt ring slides and eight for the Sloan letter slides between 20/20-20/200, and similarly for 14/14-14/140. No patient was tested to a visual acuity better than 20/20 or 14/14.

Both groups of patients had monocular acuity with the Sloan letter slides tested with occlusion of the non-tested eye. The first group of patients had monocular acuity with the modified Landolt ring slides tested under conditions of binocular vision. This was accomplished by providing the non-tested eye with only the group of diamond-shaped borders. (The slides are sold this way commercially, and this is the procedure recommended by the manufacturer.) This group is designated A. The second group of patients had monocular vision with the modified Landolt ring slides tested with occlusion of the non-tested eye. This group is designated B. For purposes of data, each eye was considered individually—thus there are 200 eyes per group.

Each group was composed of approximately equal numbers of men and women. The average age of group A was 41 years and of group B, 38 years. Since these groups are essentially equivalent in their makeup, the scores for the Sloan letter slides were combined for purposes of computing mean, median, and standard deviation.

For purposes of calculating the McNemar adaptations of the chi-square[7] the following were considered abnormal: far-20/30 or worse, near-14/35 or worse. These are the values currently used in the multiphasic health testing center. The reason for 14/35 rather than 14/21 is that this is essentially a test for presbyopia, and 14/35 is equivalent to the size of type used in newspapers.

## RESULTS

The mean far visual acuity scores (Table 2) expressed in decimal notation, are 0.91 for Sloan letters, 0.82 for the Landolt B (monocular vision) and 0.76 for the Landolt A (binocular vision). As visual acuity scores do not represent equal interval data, the median scores are probably of greater value than the mean scores in describing the central tendency of the data. The median scores are 1.00, 0.91 and 0.80, respectively.

Mean and median near visual acuity scores (Table 2) follow the identical trend, with the Sloan letter slides yielding the best

TABLE 2

STATISTICAL ANALYSIS—DECIMAL NOTATION

| | Far Vision | | | Near Vision | | |
|---|---|---|---|---|---|---|
| | Landolt A | Landolt B | Sloan | Landolt A | Landolt B | Sloan |
| No. eyes | 200 | 200 | 400 | 200 | 200 | 400 |
| Mean | .76 | .82 | .91 | .77 | .82 | .92 |
| Standard deviation | .26 | .24 | .19 | .27 | .23 | .18 |
| Median | .80 | .91 | 1.00 | .87 | .87 | 1.00 |

Correlation Coefficients: Sloan vs Landolt B
Far 0.71
Near 0.73

visual acuity scores and Landolt A the worst.

The correlation coefficients between Landolt B and Sloan targets are 0.71 for far vision and 0.73 for near.

There is a higher percentage of individuals reaching a particular acuity level on the Sloan targets than on the Landolt B targets for both near and far vision (Tables 3 and 4). Similarly, there is a greater cumulative relative frequency for the Landolt-B case than for the Landolt-A case at all acuity levels.

If a score of 20/30 or worse for far vision and 14/35 or worse for near are considered abnormal, the referral rates would be as in Table 5.

The McNemar adaptation of the chi-square (Tables 6 and 7) indicates that the probability of our observing a difference as great as that noted between the Landolt A and Sloan, and between the Landolt B and Sloan values, both near and far, due to chance alone, is less than 0.001.

## Discussion

In the report of Sloan, Rowland, and Altman,[6] comparing visual acuity achieved with Sloan letters with that achieved with Landolt rings, the product moment correlation was found to be 0.90. It should be noted that their study was done using the classic Landolt rings. The target was composed of rows of rings with breaks in the horizontal and vertical axes. The patient was required to name the position of the break in the ring. The modified Landolt rings used in the present study have breaks in the oblique axes. This should yield better scores, as most astigmatisms are on the horizontal and vertical axes. The product moment correlation between the modified Landolt rings administered in the mode which yielded the best acuity scores (Landolt-B), and the Sloan letters at far is 0.71. The problem with the modified Landolt rings appears to lie in the task of comparison and selection of the unbroken ring.

Comparison of the product moment correlation of 0.90 with that of 0.71 does not do justice to the importance of the difference in scores obtained with the classical Landolt ring and the modified Landolt ring when compared with Sloan letters. Of greater sig-

TABLE 3

Cumulative relative frequency distribution of far visual acuity scores*

| Snellen Range | Landolt | | Sloan | |
|---|---|---|---|---|
| | A | B | A | B |
| 20/20.0–29.0 | 0.60 | 0.72 | 0.85 | 0.88 |
| 20/30.0–39.9 | 0.80 | 0.85 | 0.89 | 0.94 |
| 20/40.0–49.9 | 0.84 | 0.88 | 0.94 | 0.96 |
| 20/50.0–69.9 | 0.91 | 0.92 | 0.97 | 0.98 |
| 20/70.0–99.9 | 0.96 | 0.94 | 0.98 | 0.99 |
| 20/100.0–199.9 | 0.98 | 0.99 | 0.98 | 0.99 |
| 20/200.0 or worse | 1.00 | 1.00 | 1.00 | 1.00 |
| No. of eyes | 200 | 200 | 200 | 200 |

* Decimal figures represent the proportion of eyes with this or better visual acuity.

TABLE 4

Cumulative relative frequency distribution of near visual acuity scores*

| Snellen Range | Landolt | | Sloan | |
|---|---|---|---|---|
| | A | B | A | B |
| 14/14.0–20.9 | 0.75 | 0.84 | 0.84 | 0.91 |
| 14/21.0–27.9 | 0.81 | 0.88 | 0.91 | 0.96 |
| 14/28.0–34.9 | 0.84 | 0.90 | 0.93 | 0.97 |
| 14/35.0–69.9 | 0.91 | 0.94 | 0.99 | 0.99 |
| 14/70.0–139.9 | 0.96 | 0.97 | 0.99 | 0.99 |
| 14/140.0 or worse | 1.00 | 1.00 | 1.00 | 1.00 |
| No. of eyes | 200 | 200 | 200 | 200 |

* Decimal figures represent the proportion of eyes with this or better visual acuity.

TABLE 5

Percent of patients referred as abnormal*

| | Landolt | | Sloan |
|---|---|---|---|
| | A | B | |
| Far | 40 | 28 | 12–15 |
| Near | 25 | 16 | 9–16 |

* Abnormal is defined as 20/30 or worse for far vision and 14/35 or worse for near.

TABLE 6

FAR VISUAL ACUITY—MCNEMAR TEST

| | | Landolt A | | Totals |
|---|---|---|---|---|
| | | Normal* | Abnormal† | |
| Sloan A | Normal | 118 | 52 | 170 |
| | Abnormal | 1 | 29 | 30 |
| | Totals | 119 | 81 | 200 |
| $X_1^2 = 47.11$<br>$p < 0.001$ | | | | |

| | | Landolt B | | Totals |
|---|---|---|---|---|
| | | Normal | Abnormal | |
| Sloan B | Normal | 141 | 36 | 177 |
| | Abnormal | 2 | 21 | 23 |
| | Totals | 143 | 57 | 200 |
| $X_1^2 = 28.61$<br>$p < 0.001$ | | | | |

*Normal = Better than 20/30.
†Abnormal = 20/30 or worse.

nificance is the issue of referral levels. The practical benefit to an individual participating in a screening program is limited to those designated abnormal who are able to obtain follow-up care. Reasonable referral levels are set so that serious disease will not be missed. Once this has been accomplished, changes toward better visual acuity levels can be made based on the facilities available for follow-up. If the modified Landolt rings and Sloan letters are used in a testing device, different standards of referral should be set

TABLE 7

NEAR VISUAL ACUITY—MCNEMAR TEST

| | | Landolt A | | Totals |
|---|---|---|---|---|
| | | Normal* | Abnormal† | |
| Sloan A | Normal | 168 | 18 | 186 |
| | Abnormal | 0 | 14 | 14 |
| | Totals | 168 | 32 | 200 |
| $X_1^2 = 16.06$<br>$p < 0.001$ | | | | |

| | | Landolt B | | Totals |
|---|---|---|---|---|
| | | Normal* | Abnormal† | |
| Sloan B | Normal | 180 | 15 | 195 |
| | Abnormal | 0 | 5 | 5 |
| | Totals | 180 | 20 | 200 |
| $X_1^2 = 13.07$<br>$p < 0.001$ | | | | |

*Normal = Better than 14/35.
†Abnormal = 14/35 or worse.

for the different targets. If it were decided to refer approximately 15% of those adults screened for far visual acuity, the referral level for Landolt-A would be 20/50 or worse, Landolt-B 20/40 or worse, and Sloan 20/30 or worse. This provides referral levels which are reasonable in terms of not missing pathology. Also our follow-up facilities are capable of handling the number of follow-ups generated.

There certainly are reasons to continue to use the Landolt rings. It is a good test for illiterates and those who speak a foreign language. The problem with the modified Landolt rings in these situations is that it is difficult to explain the concept of the test to those individuals.

Because of suppression, the acuity of the nondominant eye will be worse when monocular vision is tested under conditions of binocular seeing. Cook[8] identified the ability to overcome the effect of suppression as "resistance to interference." He noted that this was one of the functions of a visual acuity test which was "not pertinent to the function they attempt to measure." This is demonstrated by the fact that Landolt-B acuity is better than Landolt-A. There is no reason to test monocular vision under conditions of binocular vision, as it is a poor test of monocular vision, and a poor test of binocular vision.

The modified Landolt ring targets used for testing in this study were those which are commercially available. The tests were administered as suggested by the manufacturer. This should serve once again to make the medical community aware of the fact that there is inadequate control over the production of medical devices. We, as physicians, must evaluate testing devices in our own practices and clinics for quality control.

## Summary

Visual acuity scores of adults obtained with commercially available Sloan letters were better than those obtained with modified Landolt rings in a vision testing device used in a screening program. Scores with the Landolt rings were poorer when monocular vision was tested under conditions of binocular seeing. The number of "abnormals" referred from a screening program should be no greater than community resources available to provide follow-up can handle. The referral level must be set so that no serious pathology is missed. In order to refer equal numbers of patients with the two types of targets different levels of referral must be used. To refer 15% of those adults tested for far visual acuity, referral levels should be 20/50 or worse for modified Landolt rings testing monocular vision under conditions of binocular seeing, 20/40 or worse for modified Landolt rings testing monocular vision with occlusion of the nontested eye, and 20/30 or worse for Sloan letters. As testing binocular vision under conditions of monocular seeing is a poor test of binocular vision and lowers the level of monocular acuity, there is reason to discontinue the use of this test in this fashion.

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# LOCALIZATION OF THE HUMAN VISUAL EVOKED RESPONSE

## Early components specific to visual stimulation

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The objectives of this study were to identify components of the human visual evoked response (VER) most directly related to visual stimulation and to localize their origin by scalp recording. The approach used was to study differences in the visual evoked response to stimulation of various regions of the visual field. Early attempts at analyses of this type showed a greater correlation with handedness of the subject than with stimulation of sectors of the visual field.[1,2] More recently however, reports showing correlation of spatial visual stimulation with changes in the VER have appeared.[3-5] These reports dealt with relatively long latency components of the VER. Ciganek[6] has analyzed the VER into a primary response having the characteristics of a specific visual response and a secondary response with the characteristics of a nonspecific discharge. This analysis has received support from studies comparing recordings at scalp and cortex and after removal of visual cortex.[7] In the present study, attention was paid specifically to early components of the VER (before 100 msec) in relation to stimulation of the lateral visual half-fields.

As expected from the anatomy of the visual pathways, the maximum visual evoked responses occur in the occipital area. The distribution of the VER, however, is reportedly widespread over the scalp.[8-10] In this study, detailed spatio-temporal mapping across the scalp has been carried out of the early and later VER components in response to full-field and half-field stimulation.

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### Method

To avoid contamination of the response by rod functioning, and to minimize the effects of scattered light, the VER was recorded by stimulation in a uniformly light-adapted condition of the retina. A hemisphere one meter in diameter provided high-luminance white light adaptation at a level of 100 ft-L. The subject was positioned at the center of the hemisphere with a head and chin rest 50 cm from the stimulus light. An aperture (15-degree visual angle) in the hemisphere in front of the subject admitted light from a xenon flash lamp and reflector (Grass photic stimulator). One half of the aperture could be occluded with a white cardboard mask, presenting to the subject a half disk 15 degrees vertical by 7.5 degrees horizontal, extending to the right or left in his visual field. The aperture was backed by a red glass filter (Corning 2412) and a diffusing ground glass in front of the flash lamp. The photic stimulator was enclosed in a sound-shielded box to reduce the click attendant on the light flash. Masking noise provided by a ventilating fan on the shielded recording room made the clicks inaudible to the subject.

Standard EEG electrodes (5 mm in diameter) of the chlorided silver type were attached to the scalp with electrode cream following the International 10-20 EEG system with interpolations.[11] Monopolar recording was used with linked ear lobes as the common reference. Amplification was by differential a-c amplifiers with a band pass of 0.2 to 50 Hz. Nine channels were recorded simultaneously with a four-channel signal averager (Fabri-Tek 1052) and an

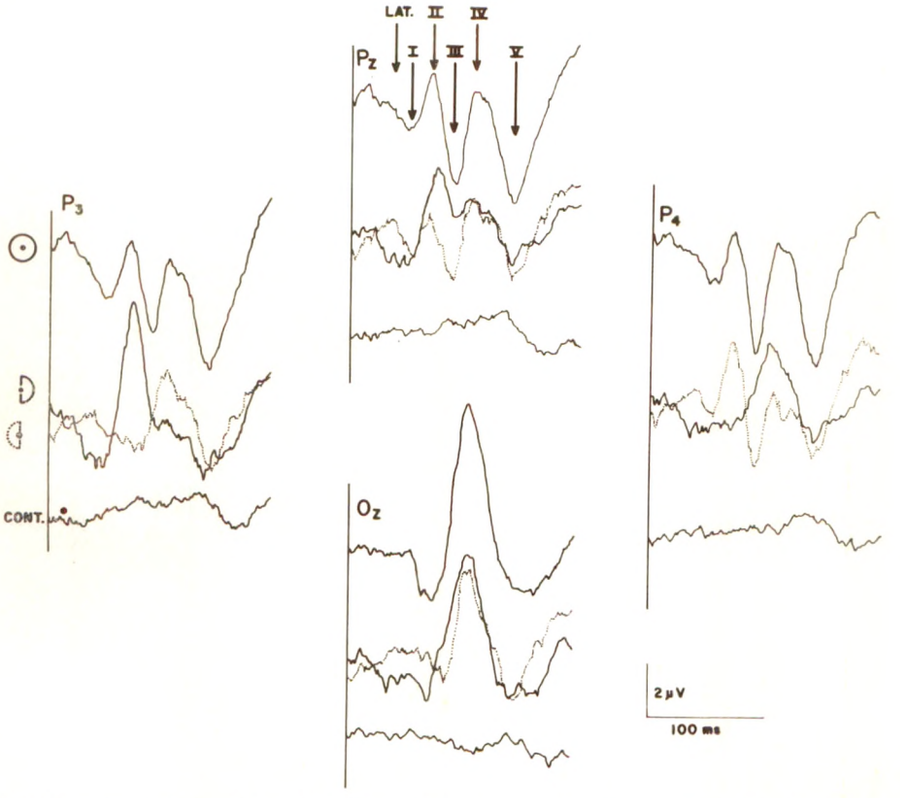



Fig. 1 (Nakamura and Biersdorf). Visual evoked responses (VER) from four electrode positions ($P_3$, $P_z$, $P_4$, $O_z$) on subject C, right eye. Top VER is full disk, next down is right half-field (solid line) and left half-field (dotted line). Bottom VER is control, with light covered. VER components are labeled at $P_z$ position (LAT. is latency). A positive potential at the labeled electrode is an upward deflection in all figures.

FM tape recorder. Responses were displayed on an x-y recorder. For contour mapping, nine channels were recorded twice. The area covered by the first recording covered electrode positions clustered around $O_z$. The second recording covered electrode positions on the periphery of the first, with one position repeated for reliability. When necessary, a third recording covered positions in the central and frontal scalp regions. Three responses were recorded and averaged from each area. The experiment was performed on six normal subjects with corrected or uncorrected vision of 20/20.

Stimulation consisted of the red stimulus light flashing at a rate of 3.3 $H_z$ for a summation of 256 flashes. The photic stimulator intensity was maintained at a constant moderate level (I-4). Stimulation was monocular, with the other eye covered by an opaque black eye patch. For full disk stimulation, fixation was on a black dot at the center of the disk. For half-field stimulation, fixation was on a black dot at the center of the vertical edge of the stimulus.

## Results

Visual evoked responses (Fig. 1) were obtained from three kinds of stimuli: full disk, left and right half-field stimulation, from four representative electrode positions ($P_3$, $P_4$, $P_z$, and $O_z$). The waveform of the VER obtained in the parietal area ($P_3$, $P_4$, $P_z$) is apparently more complex than that from the occipital pole, with earlier components found in the former. Components have been labeled at $P_z$ beginning with a negative component I at 54 msec, with successively alternating

TABLE 1

LATENCIES OF VER COMPONENTS TO FULL-DISK STIMULATION

| Subject and Eye | Latency | I | II | III | IV | V |
|---|---|---|---|---|---|---|
| C: | | | | | | |
| RE | 39 | 54 | 74 | 96 | 112 | 149 |
| LE | 35 | 54 | 74 | 96 | 115 | 144 |
| Z: | | | | | | |
| RE | 26 | 47 | 65 | 102 | 120 | 149 |
| LE | 30 | 47 | 63 | 102 | 116 | 144 |
| R: | | | | | | |
| RE | 19 | 47 | 70 | 94 | 105 | 127 |
| LE | 20 | 44 | 65 | 86 | 95 | 127 |
| M: | | | | | | |
| RE | 23 | 47 | 70 | 86 | 102 | 130 |
| LE | 23 | 47 | 70 | 91 | 102 | 135 |
| K: | | | | | | |
| RE | 24 | 40 | 69 | 103 | 117 | 139 |
| LE | 24 | 48 | 72 | 110 | 124 | 146 |
| B: | | | | | | |
| RE | 33 | 47 | 70 | 85 | 100 | 133 |
| LE | 35 | 47 | 58 | 88 | 100 | 135 |
| Mean | 27.5 | 47.4 | 68.3 | 94.9 | 109.0 | 138.1 |
| $S_x$ | 6.58 | 9.47 | 4.73 | 8.07 | 9.41 | 8.13 |

polarities; II at 74 msec, III at 96 msec, IV at 114 msec, and V at 146 msec. Mean latencies of these components at $P_z$ for both eyes of all six subjects are presented in Table 1 for full disk stimulation. As can be seen, component II is quite reliable, having the lowest variance in latency of any component.

For right half-field stimulation, component II is larger over the anatomically corresponding left cerebral hemisphere at $P_3$ than over the right ($P_4$). In contrast, component II is clearly larger over the right hemisphere for left half-field stimulation. This same relationship held for the three early components I, II, and III. Sometimes the polarity of the component was even reversed over the noncorresponding hemisphere. Control experiments show that these VER's are not artifacts of eye movements or reference electrode position.[12]

The latencies of the VER components measured at $P_z$ for the full disk stimulus, at $P_3$ for right half-field and at $P_4$ for left half-field stimulation were used as criteria for drawing potential contour maps of each component. The amplitude of each component was measured from the preceding component at these criterion latencies.

Contour maps were made for each component to the three types of stimuli for the right eye of the same subject (Fig. 2). For the full-disk stimulus, the location of the maximum potential differs from one component to the next. The focus starts near $P_3$ for component I then shifts clockwise temporally. As far as the early three components are concerned, their potential maxima occur in the parietal area with a zero crossing near the occipital pole and a polarity reversal below. The focus of the latter is not found in detail because of contamination from neck muscle potentials.

For half-field stimulation, the foci of the three early components (I, II, and III) are located over the hemisphere anatomically corresponding. When the left half-field is stimulated, the focus is over the parietal area of the right hemisphere. The zero line occurs near the occipital pole, and a reverse polarity maximum occurs in the left hemisphere opposite or below the inion. The opposite results obtain for stimulation of the right half-

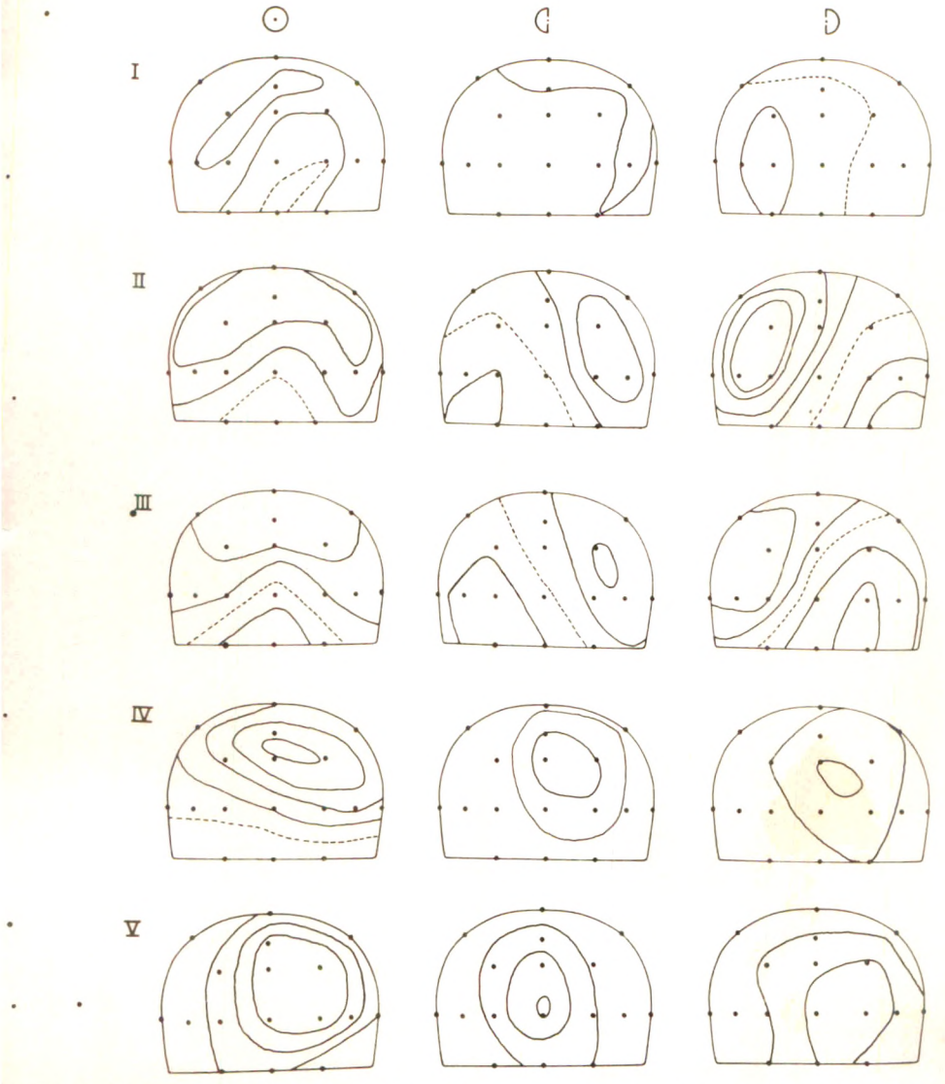



Fig. 2 (Nakamura and Biersdorf). Potential contour maps on posterior scalp for first five VER components. Subject C, right eye stimulation for full disk, right and left half-fields. Positive maxima are occipital or parietal with zero line dotted. Electrode location at the bottom midline is the inion. Moving up are electrodes at 10% distance ($O_z$), 20%, 30% ($P_z$), and 50% ($C_z$). Moving left horizontally from $O_z$ are electrodes at 15% distance, 30% ($T_5$), and 50% ($T_3$). Also shown in the upper left quadrants are electrodes $P_3$ and $C_3$. Directly below the first electrode to the left of $O_z$ is one on line horizontally with the inion. Similar positions are recorded on the right hemisphere (even-numbered). Contour lines for component I are spaced every 0.5 μv, for component II, IV, and V at 1.0 μv, and component III at 2.0 μv.

field. These results appear to hold for component I, but it is quite small under these conditions, and is more variable than components II and III. The later components IV and V did not have this relation to the side of the visual field stimulated, and very often were localized near the midline. Similar results were found for stimulation of either the right or left eyes.

VER waveform variability was found in five subjects under these experimental conditions (Fig. 3). Although intersubject variability is present, component II is clearly visible in all five subjects at position $P_z$ for full-

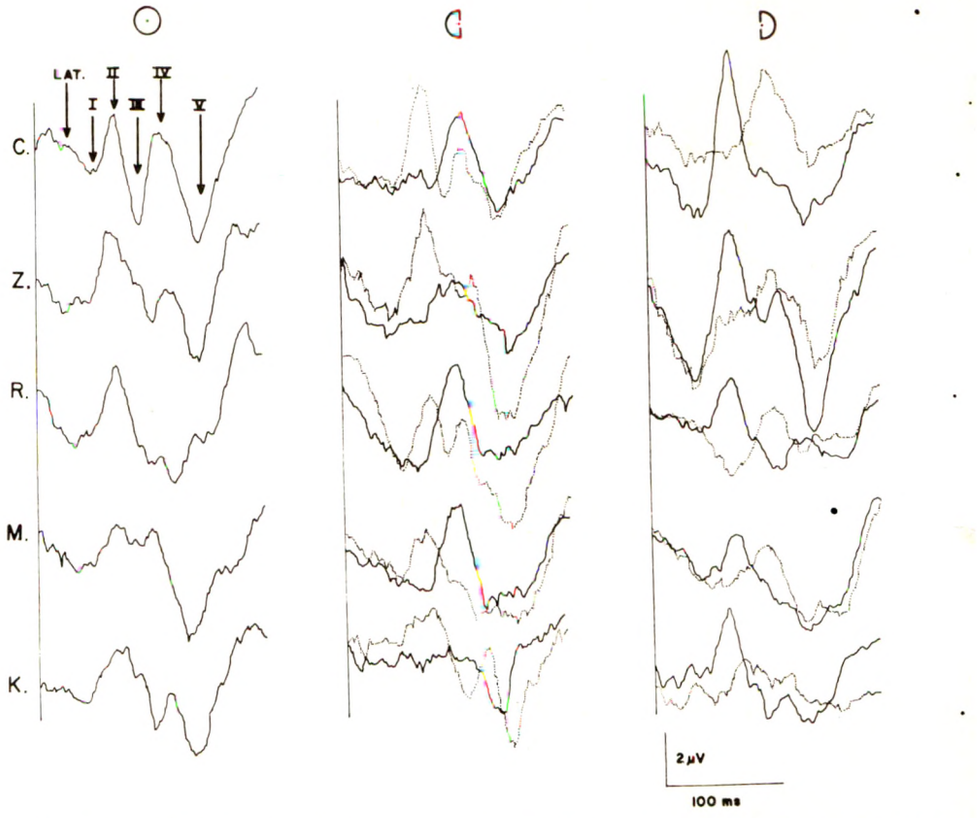



Fig. 3 (Nakamura and Biersdorf). VER's from five subjects, right eyes, for full-disk, right and left half-field stimulation. For full-disk, electrode position is $P_z$. For half-fields, positions are $P_3$ (solid line) and $P_4$ (dotted line).

disk stimulation. For half-field stimulation also, the contrast between the two hemispheres in component II for the two half-field stimuli is clearly present.

Potential contour maps on the four additional subjects for component II in response to half-field stimulation are presented in Figure 4. The similarity to the maps of subject C (Fig. 2) is evident, as is also the individual variability. Variability occurred in the position of the zero lines, the location of the positive and negative voltage maxima, and the resulting potential distribution axes. This axis was usually tilted with the horizontal, perhaps 30 to 60 degrees or more. The same relationship of the positive potential maxima to the corresponding hemisphere, however, occurred in all subjects even though this maxima might occur from the parietal to the frontal area. The contour maps for stimulation of the right or left eyes for each subject were very similar.

Contour maps for the full-disk stimulus were also variable between subjects. In general, the potential maxima of the early components was located in parietal to central areas, while the maxima of the later components were located more posteriorly. The axis of the distributions were nearly sagittal, but might be tilted slightly to one side or the other. Similar results held for the right and left eyes.

## Discussion

The study of localization of the VER is complicated by several factors. One of these

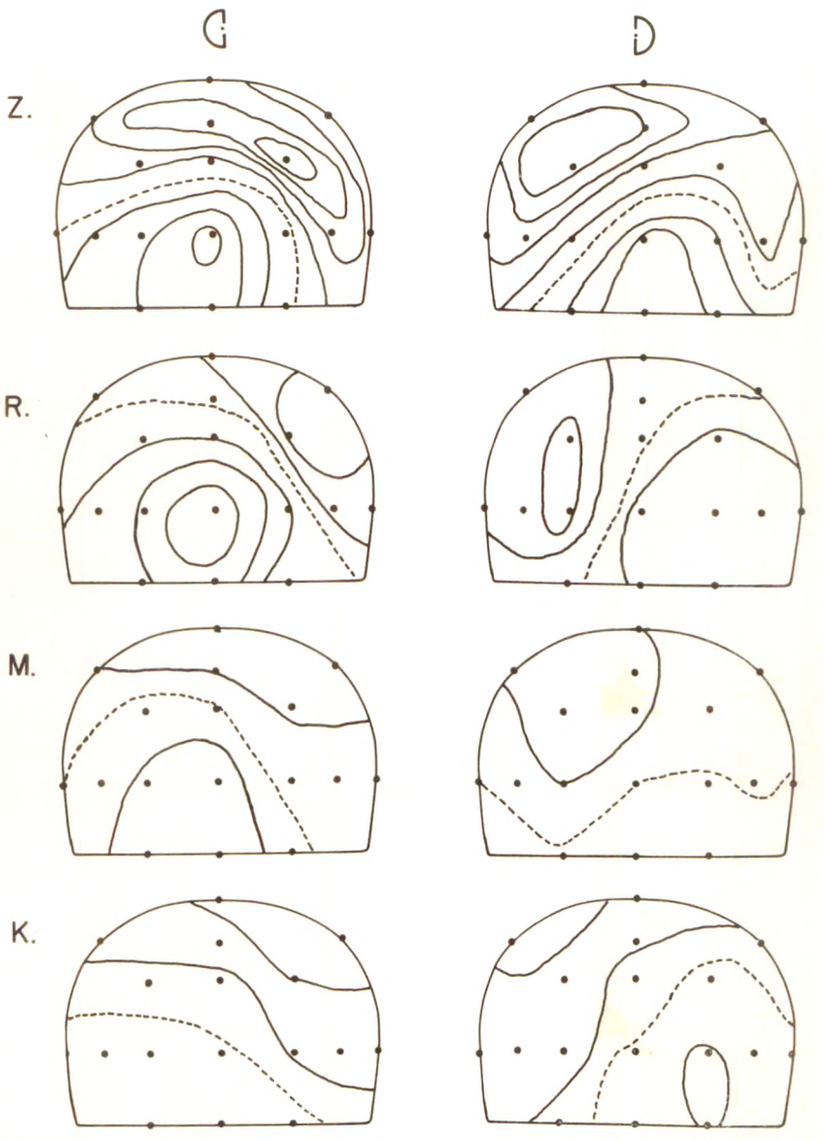



Fig. 4 (Nakamura and Biersdorf). Potential contour maps on posterior scalp from four subjects, right eyes, for right and left half-field stimulation. Maps are of component II with contour lines every 1.0 μv. The positive maxima occur forward with the zero line dotted. Electrode positions are the same as in Figure 2.

is the accessibility of various cortical areas to scalp recording. The macula, occupying a small area of the retina, is projected to a comparatively larger area of the cortex than is the extramacular retina. In addition, the macula is represented at the occipital pole while the extramacular retina is within the cortex along the calcarine fissure. Thus from anatomical considerations it might be expected that scalp potentials would be dominated by macular functioning. This is indeed true, although a number of investigators have recorded VER potentials to extramacular stimulation.[2,13-15]

The anatomical pathways to higher visual centers of man involve the semi-decussation of the optic nerve fibers. The fibers from each nasal half-retina cross at the chiasma

and run to the contralateral cerebral hemisphere while the fibers from the temporal retina run to the ipsilateral hemisphere. Therefore, a stimulus light presented to one lateral half of the visual field will be transmitted by the lens of the eye to the contralateral half-retina and the excitation will proceed to the contralateral cerebral hemisphere.

The results of this experiment with half-field stimulation show clearly that component II is maximally positive in the hemisphere receiving the primary projection pathways and smaller or negative in the other hemisphere. Indeed, the contour maps of the several components measured indicate that the three early components I, II, III (peaks at 47, 68, 95 msec) are localized in the correct hemisphere, while the later components are not so specifically localized. These three early components are thus considered "specific" to local visual stimulation and are related to what early workers have called the primary response of the VER.[6,7] Although the techniques are different, the present components I, II, and III probably correspond to Ciganek's II, III, and IV. An earlier component corresponding to Ciganek's component I was not reliably detected with the present technique. The detailed distribution for these early components for right half-field stimulation indicates a potential maximum in the contralateral parietal area ($P_3$) with a reverse polarity maximum located ipsilaterally below and to the right of the inion. The axis of this potential distribution crosses near the occipital pole. The axis is not horizontal, but tilted 30 to 60 degrees with horizontal. For stimulation of the left half of the visual field, the axis of the potential distribution shifts oppositely with the potential maximum now located symmetrically in the right parietal area (near $P_4$).

The question of intersubjective variability is always prominent with the VER. The present results are no exception. Potential contour maps were obtained on six normal subjects. Component II, the largest and most prominent among the three early components, was easily identified in some cases, but identified only with difficulty in others. The axis and gradient of the potential distributions for hemi-retinal stimulation varied between subjects. For some cases the maxima were in the parietal area ($P_3$, $P_4$), while in others the maxima occured farther forward in the central or precentral areas. The temporal shift of component loci over the scalp to full-field stimulation also varied between subjects. The qualitative results described held for all subjects, although the most detailed data was obtained from subject C, who showed large and distinct early components.

Several previous researchers have studied visual evoked responses in normal subjects by lateral half-field stimulation. Early work by Gastaut and Regis[16] appeared to find maximum potentials over the non-corresponding hemisphere. The explanation for these results can be seen in Figure 1, where the response at $O_z$ is of relatively simple waveform with the salient peaks $N_1$ and $P_1$.[17] If amplitudes are measured between $N_1$ and $P_1$, the maximum potentials may appear localized over the wrong hemisphere. The response waveform is actually more complex than this, however, as can be seen at $P_z$ or laterally over the hemispheres. Two distinct positive peaks are present (labeled II and IV) with respective preceding negative potentials (I and III). If amplitudes are measured peak-to-peak at these latencies, we find the earlier potentials are localized over the correct hemispheres for half-field stimulation. The explanation for the prior erroneous conclusion is that these early potentials tend to pass through zero potential on a phase reversal near $O_z$ and hence are unnoticed.

Normal subjects were studied by Lehmann and associates,[18] who failed to find localization for hemi-retinal stimulation in a dark room situation. They attributed this failure to stray light. In light-adapted experiments, some evidence for differences with hemiretinal stimulation was found by Eason and White.[19] Larger differences were re-

ported by Schreinemachers and Henkes,[3] also using small-spot stimuli. Recently, Cobb and Morton[5] have reported half-field differences for patterned stimulation. All of these studies have dealt with relatively long latency components of the VER. Insufficient electrode positions were used to compare with the potential distributions of the early components in this experiment.

Clinical studies on hemianopic patients support the interpretation that these localized evoked potentials result from the simulation of visual half-fields. Vaughan and associates[20] tested patients with full-field stimulation and found early components, peaking at 45 and 70 msec, to be reduced or missing over the affected hemisphere. Vaughan[17] suggested that these early components were a product of stimulation of the geniculo-calcarine pathways. Kooi and associates[21] found early EP components (peaking at 46, 72, and 93 msec) to be lengthened in latency over the affected hemisphere in hemianopes in response to full field stimulation. Regan and Heron[22] have also reported left-right amplitude differences on a homonymous hemianope with high frequency sinusoidal stimulation.

Lehmann and associates[18] recorded VERs at many electrode positions on a rare case of bitemporal hemianopia with a split chiasm. Stimulation of one eye produced a maximum-amplitude VER localized 3 cm from the midline and 6 cm above the inion on the ipsilateral hemisphere. Despite the difference in subjects and waveforms, it is interesting to compare their localization with ours. Their maximum potential was located in approximately the same position as the present results. Whether the axis of their distribution would be similar to the present results is unknown, as all their electrode positions were 3 cm or more above the inion.

The interpretation for the sources of the potentials found in this experiment can be sought by means of dipole models.[23-25] This assumes that the source can be represented by an equivalent dipole generator imbedded in a finite homogeneous spherical volume conductor. Although the amplitude and sharpness of the potential distribution is changed by assumptions of multiple shells representing the brain coverings, the basic shape of the potential distribution remains similar for a simple dipole generator.[26] Two different dipole models appear as possibilities to fit the potential distributions for the present (e.g., component II) data from half-field stimulation. The first model requires a single dipole approximately tangential to the brain surface below the occipital pole. The second model requires two radially oriented dipoles, one surface positive in the parietal area of the corresponding hemisphere, and one surface negative opposite the inion in the non-correspondng hemisphere. Both models can predict the potential maximum in the parietal area and a potential near zero at the occipital pole. The first model implies that these early VER components are generated in primary visual cortex, while the second model implies that these potentials are generated in secondary visual areas. The present data appear insufficient to decide between these possibilities. One model for the generation of the VER in the primary visual area has been proposed by Vaughan (cited in MacKay[27]).

For full-field (15-degree disk) stimulation, the three early VER components were found to reach their maxima in the midline parietal area. In this case also, an equivalent tangential dipole near $O_z$ provides a possible model for the excitation. The orientation of this dipole is approximately along the anterior-posterior axis although it may be tipped somewhat to one side. Individual differences, from both full-disk and half-field stimulation, can be represented by tilt of the dipole axis, with respect both to horizontal and to the brain surface.

Previous localization research for large area centrally-fixated stimulation has been performed by several investigators. Monnier[28] reported phase reversals in the VER with bipolar recording above and below the

inion. Cobb and Dawson[29] reported phase reversals in bipolar recording in an anterior-posterior direction at a point 3 to 6 cm above the inion for a potential peaking near 70 msec. They also reported phase reversals in the lateral direction for the same component. On the other hand, Gastaut and associates[9] found a phase reversal in the anterior-posterior direction near the occipital pole with monopolar recording. Thus, there is considerable variance in results between investigators. It was also found true in the present experiment that there was greater variability between subjects for large area stimulation than for half-field stimulation. Recent research on a foveal-sized stimulus centrally fixated by Bourne and associates[30] shows a shift in localization for successive components of the VER similar to the present full-disk results.

A variety of electrode positions have been used both in research and on clinical testing of hemianopic patients. Based on the present results, the usual $P_z$–inion bipolar placement is quite good for recording the early components from large area stimulation. For most subjects in the present study, the early components arose more from the $P_z$ position than from the inion. To test the present technique out on hemianopic patients, a double monopolar placement from $P_3$ and $P_4$ to the ears would be advantageous. As an alternative, bipolar placements from $P_3$ and $P_4$ to the inion could also be used.

## Summary

Visual evoked responses were recorded in normal subjects to full-disk (15-degree diameter) and lateral half-disk stimulation in a full-field light adapted situation. Early components of the VER, peaking at 47, 68, and 95 msec, were found to be maximal over the cerebral hemisphere corresponding to the half-field stimulated. From 17 electrode positions on the posterior scalp, detailed potential contour maps were plotted for each component. The maximum focus for the three early components occurred in the parietal to central area of the corresponding hemisphere with a potential near zero at the occipital pole. While early components of the VER were thus specific to the lateral half-field stimulated, this was not true for later components. Results were similar for either right or left eyes.

## Acknowledgment

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# PATHOGENESIS OF OCCLUSION OF THE CENTRAL RETINAL VESSELS

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The pathogenesis of central retinal vein occlusion has been a subject of great controversy since its first description by Michel[1] in 1878. The subject is of great importance, not only because of the common occurrence of retinal vascular occlusion and the marked visual disturbances associated with it, but also because a proper understanding of its pathogenesis may give a clue to the management of this condition, which has, so far, had a hopeless prognosis.

My[2-4] earlier experimental studies in rhesus monkeys on this subject showed that:

1. Occlusion of the central retinal vein at its site of exit from the optic nerve is associated with engorged and turgid retinal veins only, and with no other retinal damage.

2. Occlusion of the central retinal artery at its site of entry into the optic nerve produces immediately the classic clinical picture of arterial occlusion. Six to nine days after the occlusion, ophthalmoscopy reveals more-or-less normal retinal arteries.

3. Simultaneous occlusion of the central retinal artery and vein at their site of entry and exit from the optic nerve produces the classic clinical picture usually associated with so-called central retinal vein occlusion —i.e., retinal hemorrhages, engorged retinal veins, and retinal edema.

It was concluded from these findings that arterial ischemia is an important factor in the production of the clinical picture of central retinal vein occlusion. Other workers[5-7] have expressed similar opinions. Venous stasis retinopathy,[8] seen in conditions associated with chronic arterial insufficiency (e.g., in occlusion of the internal carotid artery,[8-12] pulseless disease,[13,15] aortic arch syndrome,[16,17] ophthalmic artery insufficiency,[18] and retinal branch arterial occlusion[19]) and resembling central retinal vein occlusion, provides further evidence in support of this view. However, this conclusion excited a good deal of controversy because: (a) there was no clinical evidence to support the finding of arterial occlusion in these cases; (b) fluorescence fundus angiography in those cases with the classic clinical picture of central retinal vein occlusion did not show any arterial occlusion[7,20,21]; and (c) in pure central retinal vein occlusion unassociated with hemorrhagic retinopathy, the question of where the blood pumped in by the artery goes still remained to be answered.

In order to explain the discrepancy between the experimental results and the fluorescence fundus angiographic findings in patients, I have investigated the fallacies in interpretation of the angiographic studies in retinal vascular occlusive disorders in man. The crucial question to be answered in the fluorescence angiographic studies of such cases is whether the inability to demonstrate a block in the retinal arteries in such studies is a true index of the absence of arterial occlusion or not. The mechanism of restoration of flow in cases with central retinal artery occlusion and the pathogenesis of the hemorrhagic retinopathy associated with retinal vascular occlusion are discussed.

## OBSERVATIONS AND COMMENTS

### CENTRAL RETINAL ARTERY OCCLUSION

The presence of normal retinal arterial circulation on fluorescence angiography may be thought to exclude the existence of a retinal arterial occlusion. The following three cases are presented as examples to demonstrate the fallacies of such a conclusion in many cases.

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## Case reports

*Case* 1.—A 27-year-old man was seen in the casualty department with a four-day history of "inability to see the tip of his nose on closing the left eye." On examination, the visual acuities in both eyes were 6/5. The right eye showed keratic precipitates (KPs), mild flare and a few cells in the anterior chamber; cells in the vitreous; and evidence of superior temporal retinal arteriole occlusion distal to a patch of acute choroidal retinitis over which the arteriole crossed. There was retinal edema in the area involved.

Fluorescence fundus angiography that day revealed an almost complete occlusion of the arteriole (Fig. 1-A), with only a minute trickle of fluorescein beyond the block very late in the transit of the dye (Fig. 1-B). Interestingly, the patch of choroiditis revealed by intense leakage of fluorescein was seen to be many times bigger than the one seen ophthalmoscopically (Fig. 1-C). Thus, the ordinary ophthalmoscopically visible patch of choroiditis is just the tip of an iceberg lying underneath.

The patient was treated with systemic corticosteroids. The chorioretinitis lesion responded very well to this therapy. Three months after the onset of the trouble, when the choroiditis had completely cleared, fluorescence fundus angiography was repeated. No block in the originally occluded arteriole was seen (Fig. 1-D), and a normal retinal circulation was seen in the area involved. A permanent destruction of the choroid in the center of the patch of choroiditis was seen.

This case shows the importance of the time elapsing between the onset of the arterial occlusion and the carrying out of the angiographic studies. Though, at the beginning, the arteriole was completely occluded, later on a normal circulation was seen. If this patient had not been seen for some months after the occlusion, investigations by fluorescence fundus angiography for the inferonasal field defect would have shown the presence of normal circulation, which would have excluded completely a diagnosis of arterial occlusion as the cause of the field defect.

*Case* 2—A 58-year-old man was seen with a history of sudden onset of defective vision in the left eye three days previously. On ophthalmoscopy, he showed a classic fundus picture of central retinal artery occlusion, with a cherry red spot in the macular region and his visual acuity in that eye was reduced to the perception of light only. The other eye was perfectly normal. His blood pressure was 230/130 mm Hg. Fluorescence fundus angiography that day revealed a normal dye transit, with the retinal arterioles starting to fill 8.5 seconds after the injection of fluorescein and emptying in 16-17 seconds after the injection. The retinal vascular tree, including the capillaries, filled normally (Fig. 2).

Although this patient showed the classic clinical picture of central retinal artery occlusion, fluorescence angiography revealed a perfectly normal retinal circulation with no abnormality of any kind. The transitory block in the artery was most probably the result of a spasm due to arterial hypertension.

*Case* 3—A 14-year-old girl was attending the Eye Outpatient Department because of herpes zoster ophthalmicus of the left side. Her visual acuity, which had been normal despite her disease, suddenly became defective in the left eye. When seen about 24 hours later, she had a classic clinical picture of central retinal artery occlusion with a small normal area of the retina temporal to the optic disk because of a patent cilioretinal arteriole. Nine months later, fluorescence fundus angiography was performed. The central retinal artery of the left eye filled normally (Fig. 3-A), though the arterial phase was slightly prolonged. She showed a complete absence of the usual arteriovenous phase (Fig. 3B). In this eye, the small retinal veins started to fill only after the arterial phase was over (Fig. 3-B) and the venous phase was very much prolonged (Fig. 3-C). I have called this phenomenon "hibernation of the blood in the retina," because in between the arterial and the venous phase the blood hibernates somewhere in the retina to emerge slowly and fill the veins gradually. Cilioretinal anastomoses were prominent on the disk and peripapillary retina (Fig. 3-A).

This patient also showed a normal arterial filling in spite of having had an undisputed central retinal artery occlusion nine months previously.

From these three examples, and based upon the findings of the studies in which these cases were investigated, it could be concluded that in fluorescence fundus angiography the presence of a normal retinal circulation by no means excludes the previous occurrence of a retinal arterial occlusion. A review of the fluorescence fundus angiographic studies in retinal arterial occlusion reported in the literature confirms this conclusion,[20-24] although not much significance seems to have been attached to this observation. Thus, in central retinal artery occlusion, a few hours or days after the onset of the occlusion, circulation is almost always seen on fluorescence fundus angiography; the amount of flow increases with the pas-

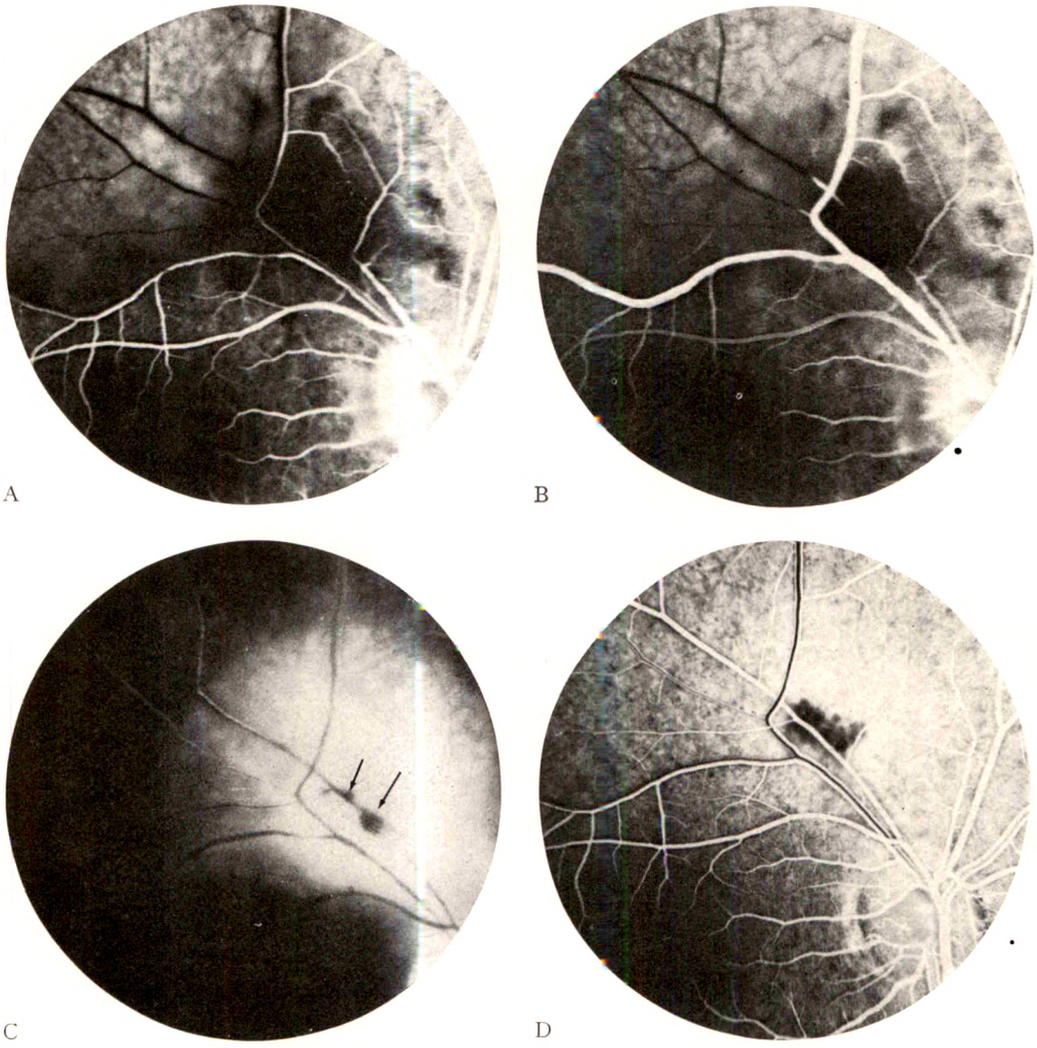



Fig. 1 (Hayreh). Fluorescence fundus angiograms in a 27-year-old man with occlusion of superior temporal artery secondary to a patch of acute choroidoretinitis. Views (A), (B) and (C) were taken four days after the occlusion, and (D) three months after the occlusion. (A) Arteriovenous phase, showing occlusion of superior temporal artery and the area supplied by it. The nonfluorescent area at the site of occlusion corresponds to the ophthalmoscopically visible patch of acute choroidoretinitis. (B) Venous phase, showing a small trickle of dye in the occluded artery. (C) Late phase, 15 minutes after the injection of dye, showing marked fluorescence of the area of choroidoretinitis (compare the size with that of the arteriovenous phase), with some filling of the vessels in the occluded area. Two hemorrhages (arrows) were seen on the ophthalmoscopically visible patch of choroidoretinitis. (D) Arteriovenous phase, taken three months after the occlusion, showing normal filling of the superior temporal artery and the area supplied by it. Nonfluorescent patch on the artery represented the healed patch of choroidoretinitis.

sage of time and, in late cases, returns more or less to normal. The time taken for the retinal arterial circulation to re-establish itself varies in different individuals, depending upon the cause and site of the arterial occlusion, the collateral channels available and, possibly, other factors, which are discussed below.

A partial occlusion of the central retinal artery, sufficient to produce the typical ischemic retinal changes, is a possibility in some of the cases where angiography shows the presence of some circulation.

The vascular tissue of the retina is far more resistant to anoxia than the retinal neural tissues.[25] This would produce irreversibly damaged and atrophic neural tissue in the retina with a practically normal-appearing retinal vasculature. The late ophthalmoscopic appearance of the fundus in such cases may be within normal limits or may show optic atrophy with attenuated retinal vessels.[21]

## Mechanism of restoration of arterial circulation in central retinal occlusion

The subject has important implications in

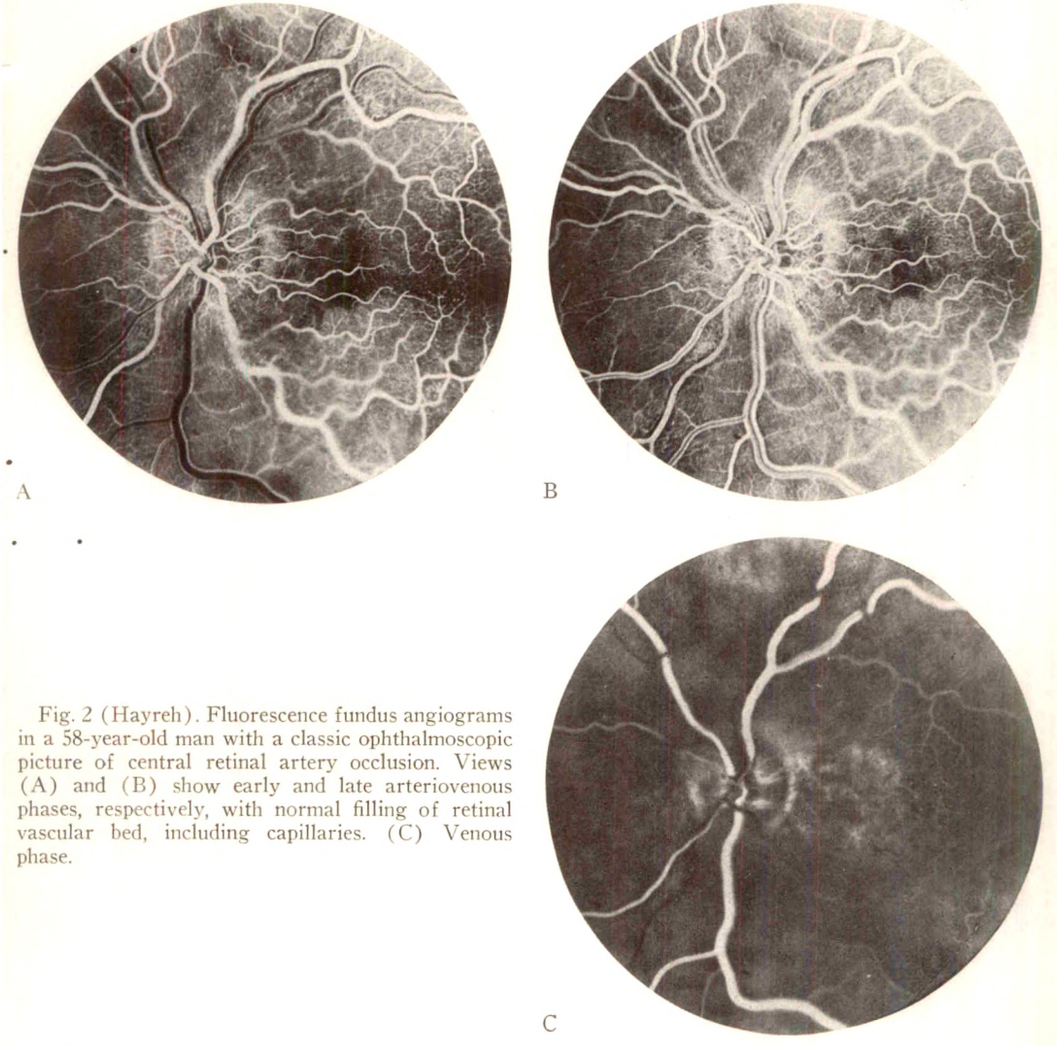
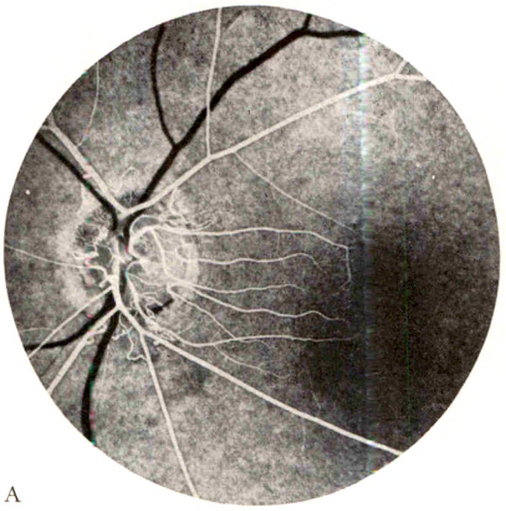
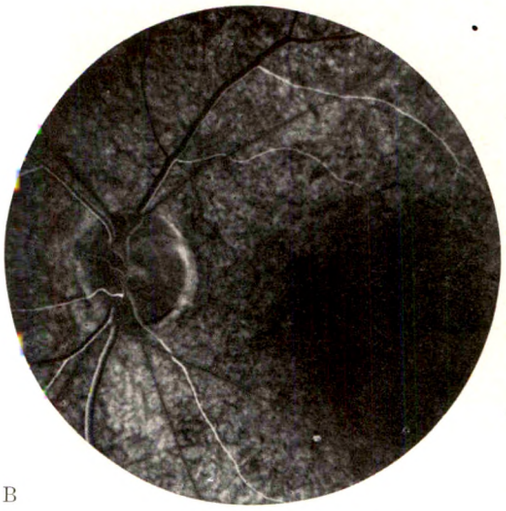


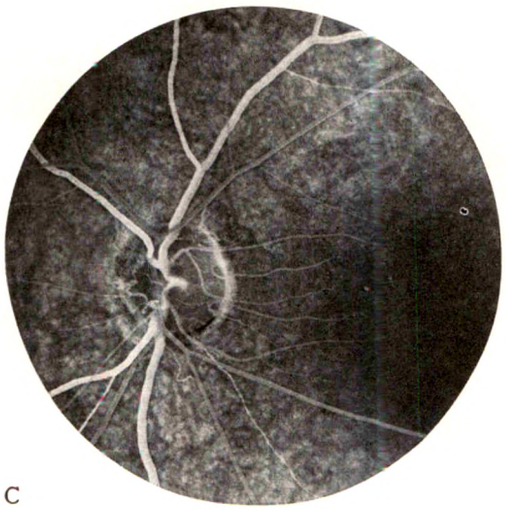
Fig. 2 (Hayreh). Fluorescence fundus angiograms in a 58-year-old man with a classic ophthalmoscopic picture of central retinal artery occlusion. Views (A) and (B) show early and late arteriovenous phases, respectively, with normal filling of retinal vascular bed, including capillaries. (C) Venous phase.



A



B



C

Fig. 3 (Hayreh). Fluorescence fundus angiograms in a 14-year-old girl who had central retinal artery occlusion nine months previously and had a patent cilioretinal artery. (A) Arterial phase, showing cilioretinal anastomoses at the optic disk and adjacent retina. (B) Phase in between the arterial and venous phase showing "hibernation" of the blood in the retina and the start of filling of the retinal veins. No arteriovenous phase was seen. (C) Venous phase.

a consideration of the outcome of treatment and prognosis of cases with such an occlusion. The circulation in the central retinal artery after occlusion may be re-established by any of the following mechanisms:

*Disappearance of spasm of the artery*—In hypertensive arterial disease and in some traumatic cases, occlusion of the central retinal artery may be due to a spasm of the artery. Disappearance of the spasm spontaneously or after the use of vasodilators would restore the circulation. In such cases the circulation is likely to re-establish within a few minutes to a few hours. The second case cited above appears to belong to this category, where the occlusion lasted sufficiently long to give rise to a typical retinal artery occlusion picture and the disappearance of the spasm later on restored the normal retinal circulation.

*Dislodgement of an embolus*—In cases where an embolus in the central retinal artery or one of its branches is responsible for the occlusion, its dislodgement would lead to a restoration of the retinal circulation within a few minutes or a few hours of the occlusion. Such instances are well known to persons familiar with the subject.

*Recanalization of the blocked lumen*—In thrombosis, this may be due to (1) contrac-

tion of the thrombus owing to the fibrin which it contains, leaving a space between it and the vessel wall; this occurs more commonly in venous than in arterial thrombosis. (2) A part of the thrombus may absorb owing to the activity of the leukocytes; and (3) by canalization of a thrombus. The first case mentioned above belongs to this category.

*Establishment of collateral anastomoses*—In any discussion of the subject, I find little mention of the collateral anastomoses available in the event of central retinal artery occlusion. For a proper understanding of the various anastomoses available, a brief account of the anatomy of the central retinal artery is desirable. A detailed study of the anatomy of the artery[26-28] shows that the artery at two sites during its entire course lies in rigid surroundings where it cannot alter its size and shape and shows a constriction in its lumen; these sites are: (1) where it pierces the dura mater of the sheath of the optic nerve to enter the sheath (Fig. 4), and (2) when it passes through the rigid lamina cribrosa.

Of the two constrictions, the narrowest lumen of the central retinal artery seems to be where it pierces the dura mater. The chances of an embolus which enters the central retinal artery from the ophthalmic artery becoming impacted at this site are probably higher than when it passes through the lamina cribrosa. Therefore, it seems most probable that in cases of central retinal artery occlusion due to embolism, the block will be at the first site, and in cases with occlusion due to thrombosis the block could be at either of these or at other sites.

The site of occlusion is very significant because this determines the anastomotic channels available to re-establish the circulation of the central retinal artery. During its intraorbital course, the central artery has practically no anastomoses. During its intravaginal course, it gives out pial branches in 95% of cases. The pial branches in the great majority of cases establish prominent anastomoses with other pial branches arising




Fig. 4 (Hayreh). Transverse section of a human optic nerve at the site of penetration of the dural sheath by the central retinal artery. It shows the artery lying in the dura. CRA = central retinal artery. D = dura mater. ON = optic nerve.

from the peripapillary choroidal vessels, the arterial circle of Zinn and Haller, the main ophthalmic artery, and other orbital arteries. These pial anastomoses of the central retinal artery have been described and illustrated in detail elsewhere.[26,28,29] The pial anastomoses, being prominent, can play a very important role in establishing collateral circulation. During its intraneural course, the central artery establishes in some cases minor anastomoses which are not of significance in establishing a collateral circulation. At the lamina cribrosa, the central artery gives out no branches, hence there are no anastomoses by the artery at this site. Thus, the pia of the optic nerve is the only site where any anastomoses are seeen that are of significance in establishing a collateral circulation. In cases where the site of occlusion in the central retinal artery is somewhere between its origin and its entry into the dura—i.e., before the origin of the pial branches—the pial anastomoses are available to establish some degree of circulation in the majority of cases. In these cases the traditional treatment of the central retinal artery occlusion with vasodilators would help to dilate these collaterals and establish circulation in the artery distal to the block. These cases can easily be confused with cases of spasm of the artery.

On the other hand, when the block occurs

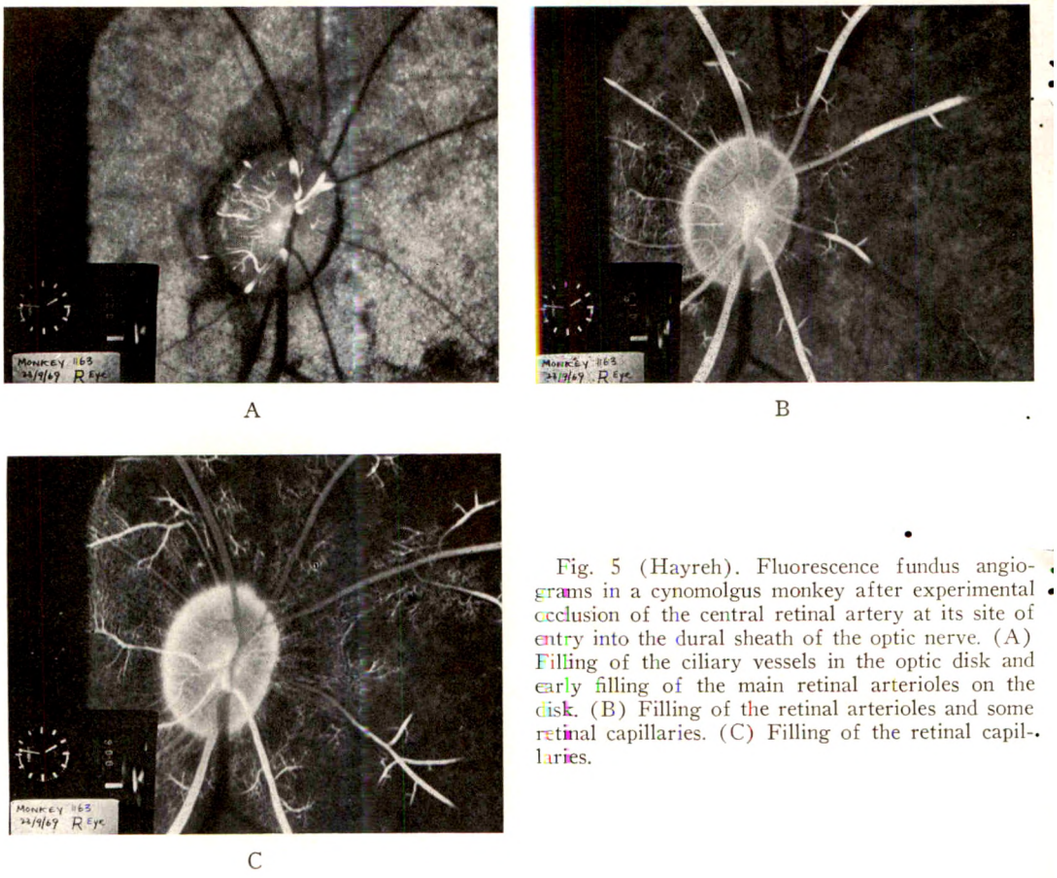



Fig. 5 (Hayreh). Fluorescence fundus angiograms in a cynomolgus monkey after experimental occlusion of the central retinal artery at its site of entry into the dural sheath of the optic nerve. (A) Filling of the ciliary vessels in the optic disk and early filling of the main retinal arterioles on the disk. (B) Filling of the retinal arterioles and some retinal capillaries. (C) Filling of the retinal capillaries.

during the intraneural part or at the lamina cribrosa, the pial collaterals are of no help in establishing the circulation. The prognosis in such cases is grave and no treatment is likely to be of any use. Thus, in any discussion of the prognosis and outcome of the treatment of central retinal artery occlusion, the site of occlusion, which determines the availability of the collaterals, is very important. Treatment with vasodilators, whether by retrobulbar injection or by other routes, is of help only when the occlusion is in the intraorbital part of the artery (up to its site of entry into the dural sheath of the optic nerve) and is useless in cases with intraneural block.

Since, in cases with central retinal artery occlusion, it is impossible to be definite about the site of occlusion, the above discussion may seem theoretical and pointless. The presence of pial anastomoses in the vast majority of cases, however, indicates that it would seem justifiable to try vasodilators in all cases, especially those suspected of being occluded by embolism or spasm.

It is possible that, in some of the cases of central retinal artery occlusion studied by fluorescence angiography by various authors, one of the modes of an early restoration of circulation may be through the pial anastomoses.

Fluorescence angiography in monkeys, after experimental occlusion of the central retinal artery (at the site of its entry into the sheath of the optic nerve) revealed that the retinal arterioles filled to a varying extent at the optic disk from the ciliary vessels supplying the disk via their communications with the surface vessels of the disk (Fig. 5).

Such a phenomenon was also suggested by the cilioretinal anastomoses seen in the third case reported above.

### Central retinal vein occlusion alone

Findings similar to those in experimental studies with central retinal vein occlusion[2-4] alone have been reported in patients. The following patient and Case 5 are cited as examples.

#### Case report

*Case* 4—A 62-year-old man went to his optician for a routine testing of his glasses. The optician noticed abnormal retinal vascular changes in his left fundus and referred him to an ophthalmologist. The patient himself had no symptoms, but he remembered an episode of blurred vision in his left eye about a year previously. He gave a history of ischemic heart disease of 10 years' duration.

On examination, the visual acuity was 6/5 in the right and 6/6 in the left eye with correction. On ophthalmoscopy, the left fundus showed markedly distended and tortuous retinal veins, new vessels on the disk and the adjacent retina, blurred disk margins, and no retinal hemorrhages. The right fundus was normal. He was diagnosed as having "incipient central retinal vein occlusion" on the left side. A thorough physical examination revealed no systemic abnormality. In view of the blurred margins of the left disk, the neurologists considered the possibility of his having an intracranial space-occupying lesion.

Fluorescence fundus angiography revealed markedly sluggish circulation in the left retinal veins as compared to the right side. The left optic disk and the adjoining retina showed dilated vessels and microaneurysms. No evidence of edema of the optic disk was detected. The right fundus showed no abnormality.

Nineteen months later, with the left fundus showing the same ophthalmoscopic and fluorescence angiographic changes, the patient still had no complaint and his visual acuity was normal.

In this patient, an accidental discovery of the retinal venous obstruction by an optician, where there were no visual symptoms and absence of retinal haemorrhages, shows typically the course of events in a pure central retinal vein occlusion. The dilated vessels on the optic disk and adjacent retina most probably short-circuited the retinal blood via the disk vessels to the choroidal circulation without actually developing into prominent retinociliary veins.[30] During the ensuing 19 months there was no change.

This type of case, with pure central retinal vein occlusion behind the optic disk and unassociated with arterial ischemia, is usually considered as incipient central retinal vein occlusion. In these cases, the blood is short-circuited to the choroidal bed via the connections of the central retinal vein with the choroidal circulation at the optic disk. The presence of the prominent retinociliary veins at the optic disk in cases with venous obstruction confirms this view.[30] In fact, one of the major objections raised to my original hypothesis[2-4] was the problem of where the blood from the retinal veins drains to in the pure central retinal venous occlusion unassociated with hemorrhages and other pathology. Fujino and his associates[7] reported that experimental occlusion of the central retinal vein on the optic disk in monkeys resulted in hemorrhagic retinopathy when the above-mentioned collaterals at the disk were also occluded and no collateral channels for shortcircuiting the blood were left. They rightly pointed out that the sequence of events is: increased venous pressure, which is then transferred across the capillary bed to the arterial side, resulting in stoppage of the arterial circulation, which produces ischemia and hemorrhagic retinopathy.

In pure central retinal venous occlusion, there is no visual disturbance or retinal damage. According to Kohner and her associates,[31] the retinal cells can survive venous occlusion because of the presence of arterial inflow, a high pressure head driving collateral flow and more distensible vessels.

### Combined retinal arterial and venous occlusion

The following case is unique in that it provides the missing clinical proof of the important role played by arterial ischemia in the production of the clinical picture of classical so-called retinal venous occlusion.

#### Case report

*Case* 5—A 66-year-old man had an attack of blurred vision in the left eye which lasted for about 20 minutes. Nineteen days later he had another similar attack of blurred vision in the same eye lasting for about 15 minutes. On waking up next morning

he found his vision again blurred. When seen four or five hours later, his visual acuity in that eye was 4/60. His fundus showed markedly engorged and turgid retinal veins with new vessels on the disk, normal retinal arterioles, and a few small retinal hemorrhages (Fig. 6-A). A diagnosis of "incipient central retinal vein occlusion" was made by the consulting ophthalmologist.

Fluorescence fundus angiography six or seven hours after he had noticed the defective vision showed a normal filling of the retinal arterioles (Fig. 6-B), the arterial phase being prolonged by four seconds as compared to his normal eye. The area between the optic disk and macula showed a complete absence of retinal capillary filling because of occlusion of the cilioretinal artery supplying that area (Fig. 6-B and C). No arteriovenous phase was seen, i.e., the phenomenon of "hibernation of the blood in the retina" (vide supra) was seen (Fig. 6-C and D). Small retinal veins started to fill 12 seconds after the filling of the arteries, as compared to less than two seconds in the normal eye. The veins did not empty completely even in two minutes, as compared to 30 seconds in his normal eye. Prominent retinociliary veins[30] were seen on the disk which ophthalmoscopically were diagnosed as new vessels (Fig. 6-E). These retinociliary veins evidently acted as collateral channels to drain away the blood from the retinal veins to the choroidal veins.

When the patient was seen two weeks later, his visual acuity was 6/9 in that eye and he had a patch of retinal hemorrhages in the area supplied by the occluded cilioretinal artery (Fig. 6-F), with no change in the rest of the fundus. Visual fields revealed an enlarged blind spot which corresponded to the area of the retinal hemorrhages. Fluorescence angiography three weeks after the first angiography when his visual acuity was 6/6-part, revealed a filling of the cilioretinal artery. His fundus still showed the distended veins and the patch of retinal hemorrhages. When seen three months after the occlusion, his visual acuity was 6/9, the fundus showed no hemorrhages but the engorged veins showed no change. The other eye was normal at all times.

This patient had a chronic central retinal vein occlusion, which produced engorged and tortuous retinal veins with development of collateral retino-ciliary veins on the disk, which shunted the retinal blood to the choroidal circulation, but his visual acuity was not affected. The occlusion of the cilioretinal arteriole in that eye brought on the defective vision and the block was demonstrated angiographically six to seven hours after the onset. At that time no retinal hemorrhages were seen, though some retinal edema in that area was present. At this stage, in view of the retinal venous changes, the patient was erroneously diagnosed as having an "incipient central retinal vein occlusion," and his defective vision was attributed to that. When seen a fortnight later, the area which suffered the arterial insufficiency developed the hemorrhages and the clinical picture of so-called localized venous occlusion, while the rest of the retina showed no similar change, in spite of generalized venous changes. As the localized retinal edema (which also involved the macula) settled, his visual acuity returned to near normal. This eye, thus, provided an ideal experimental model where a localized retinal arterial insufficiency was superimposed by nature on a generalized retinal venous congestion. This resulted in a localized picture of the so-called retinal venous occlusion in the area of arterial ischemia and loss of retinal function localized to that area; in spite of the marked venous engorgement the rest of the fundus showed neither any loss of function nor the changes which are typically described as central retinal vein occlusion. A similar case is reported by Oosterhuis.[6]

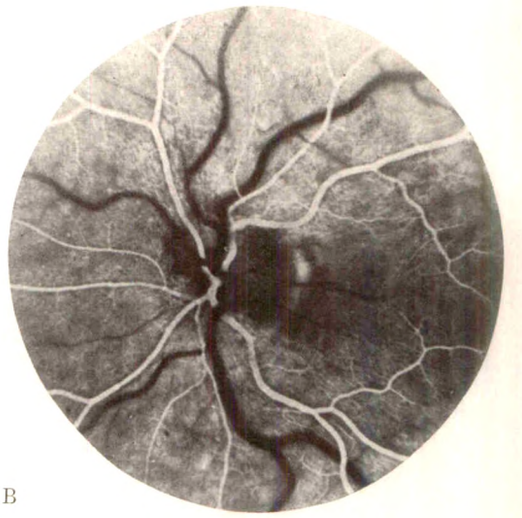
These two very instructive cases leave lit-

➤

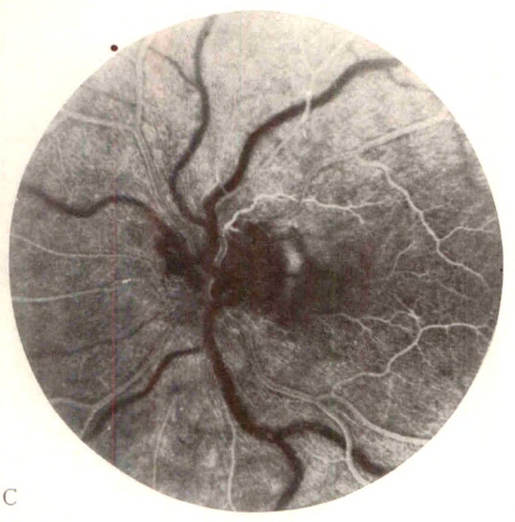
Fig. 6 (Hayreh). Fundus pictures and fluorescence fundus angiograms in a 66-year-old man with chronic retinal venous obstruction and superimposed cilioretinal arteriole occlusion. Fundus picture (A), and fluorescence fundus angiograms (B through E) were taken six or seven hours after the occlusion of the cilioretinal arteriole. Views (B) and (C) are early and late arterial phases, respectively, showing normal filling of retinal arterioles with a patch of complete absence of filling of retinal vessels in the area supplied by the cilioretinal arteriole. Views (D) and (E) show early and the late venous phases, respectively. Note the absence of arteriovenous phase, indicating the "hibernation" of the blood in the retina. View (F) is a fundus picture taken two weeks after (A), showing retinal hemorrhages in the area of the occluded cilioretinal arteriole (compare with first fundus picture, top left).



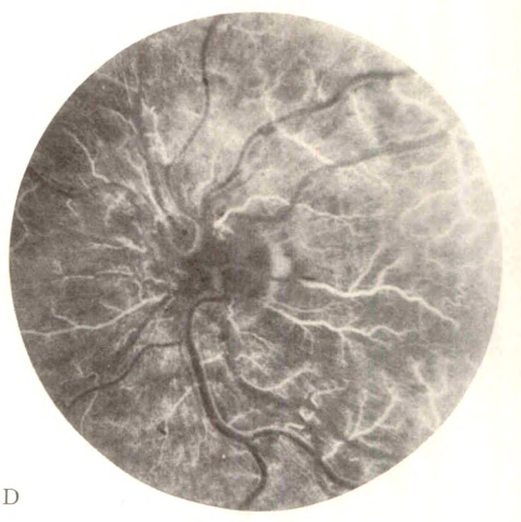
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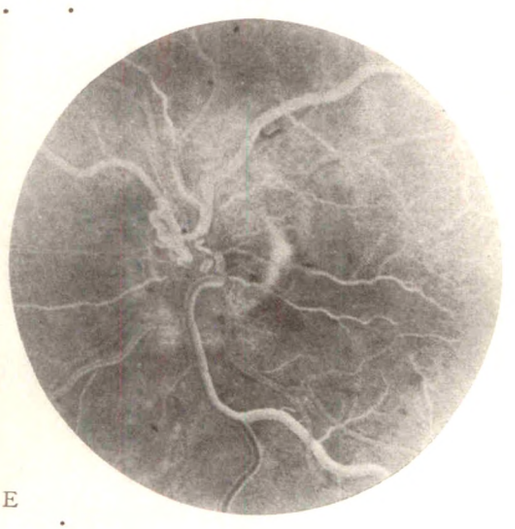
B



C



D



E



F

tle doubt about the mechanism of the so-called retinal venous occlusion, and firmly establish that arterial ischemia, whether transitory or prolonged, is absolutely essential for the production of the clinically identifiable entity of the so-called retinal vascular occlusion. These cases, thus, should be called "retinal vascular occlusion" and not "retinal venous occlusion." On the other hand, patients often diagnosed as having partial or incipient venous occlusion represent cases with true central retinal venous occlusion.

As stated previously, unless the fluorescence fundus angiography is performed during the first few hours of the occlusion in these cases, the chances of seeing an arterial block are remote. This inability to demonstrate the arterial occlusion in such cases [7,20,21] has been a major cause of the confusion created by fluorescence angiography and the doubts cast on the mechanism of retinal vascular occlusions, which has been suggested by experimental studies.[2-4,7] Since most central retinal vein occlusion cases are seen very late and, in the majority, it is not possible to get any definite history of the time of onset, the inability to see the block in the arteries on angiography in no way contradicts the above hypothesis. The other factor to be borne in mind is the presence of a transitory ischemia due to a spasm or transitory embolus or similar process in such cases, which may act as a trigger in the presence of existing venous congestion. Since the retinal venous congestion itself causes no symptoms, the patients seek advice only when the insult of arterial ischemia is superimposed. This transitory ischemia may be a factor in determining recovery of good vision in some cases with central retinal vascular occlusion.

My studies, although they support the views of Rubinstein[5] on the importance of arterial insufficiency in central retinal vein occlusion, do not agree with his conclusion that there is no venous block in such cases. His inability to find a venous block seems to have been due to restoration of the venous circulation by the time fluorescence angiographic studies were performed. Such a restoration of circulation has been reported by Hill.[21] My studies indicate that, for the production of hemorrhagic retinopathy, occlusion of both the artery and vein is essential, though these cases at a later stage may show neither arterial nor venous block on fluorescence angiographies.

## Pathogenesis

Klien and Olwin[32] and Klien[33] postulated the following three occlusive mechanisms involved in occlusion of the central retinal vein: (1) Occlusion by external compression by sclerotic adjacent structures and secondary endothelial proliferation. (2) Occlusion by primary venous wall disease, either degenerative or inflammatory in nature. (3) Hemodynamic disturbances may be produced by a variety of factors, e.g., subendothelial atheromatous lesions in the central retinal artery, arterial spasm, sudden reduction of blood presssure, blood dyscrasias, possible reflex vasoconstriction of the central retinal vein, etc., and further aggravated by arteriosclerosis or unfavorable anatomic relations. These produce stagnation of the flow in the vein and result in primary thrombus formation.

A consideration of Virchow's[34] triad is essential in a discussion on the mechanism of thrombocytosis. The three factors of the triad are as follows:

*Slowing of blood stream*—This is particularly important in venous thrombosis.

*Changes in vessel wall*—The arteries, because of the common occurrence of atheromatous changes, are more commonly affected by this factor. The atheromatous changes predispose to thrombosis because of roughening of the smooth intimal surface and also by producing narrowing of the lumen, which slows the blood stream.

*Changes in the blood*—In thrombocytosis, this is perhaps the most decisive, though least known factor.[35] This may involve stickiness of platelets, viscosity of the blood, or the heparin content.

In cases with combined arterial and venous occlusion in the retina, most probably the sequence of events is: the arterial occlusion (partial or complete, transitory or prolonged) leads to slowing down or stoppage of the circulation in the retinal vascular bed, which, in turn, leads to venous stasis. The venous stasis in a susceptible individual precipitates venous thrombosis. This is further suggested by the fact that most of these episodes come on during sleep when there is a systemic arterial hypotension. Systemic arterial hypotension, with or without arteriosclerotic changes in the central retinal artery, would slow down the retinal circulation. Not only that, but the hypotension could also precipitate central retinal artery thrombosis, because the development of arterial thrombosis in arteriosclerotic individuals with arterial hypotension is well documented in cerebral artery thrombosis. This is further suggested by a large number of reports in the literature establishing a close relationship between central retinal vascular occlusion and arteriosclerotic changes and arterial hypertension.[3]

In any consideration of retinal circulation, the importance of the intraocular pressure must be borne in mind. The retinal vessels are constantly subjected to the intraocular pressure. The venous stasis produced by the fall of pressure in the retinal circulation is further aggravated by the intraocular pressure, particularly when the pressure is raised above normal. This would be an additional important factor in the causation of thrombosis. The commonly observed association between central retinal vein occlusion and glaucoma supports this view. In addition to inducing venous stasis, the raised intraocular pressure may also aggrevate retinal ischemia in cases with low blood pressure in the retinal circulation. An interesting finding in these cases is that the intraocular pressure on the occluded side is usually lower than on the nonoccluded side[2,36-39]; the mechanism of this, however, is obscure.

In some cases, primary retinal venous obstruction in the closed retinal circulation may produce secondary retinal arterial insufficiency,[7] particularly in arteriosclerotic and susceptible individuals, and result in arteriovenous occlusion.

Arterial ischemia damages the vascular wall and produces ischemic capillary changes, so that the capillaries are not able to withstand the blood pressure on restoration of arterial circulation; this leads to hemorrhages, resulting in hemorrhagic retinopathy.

In cases which already have a venous block, as in Case 6, superadded arterial ischemia results in a combined vascular occlusion, and produces the typical hemorrhagic retinopathy.

## Conclusions

Occlusion of the central retinal vein alone produces no retinal damage and, in late cases, is associated with the establishment of collaterals which help to drain the blood away to other patent channels, particularly via the retinociliary connections at the optic disk; the visual acuity is unaffected.

Occlusion of the central retinal artery alone produces white infarct of the retina.

A combined occlusion of the central retinal artery and vein in the retina results in a hemorrhagic infarction of the retina which, in the past, has been erroneously attributed to a simple retinal venous occlusion. In view of this, it is suggested that the term "central retinal vascular occlusion" should be used in these cases.

On fluorescence fundus angiography, the inability to demonstrate an arterial block in cases with central retinal arterial or arteriovenous occlusion does not indicate that the artery was not previously blocked. This is because the arterial circulation re-establishes itself within a few hours or days. The prominent pial anastomoses established by the central retinal artery play an important role in restoration of the circulation; the site of occlusion, however, determines the availability of these anastomoses.

The sequence of events in retinal arterio-

venous occlusion most probably is: arterial occlusion (partial or complete; transitory or prolonged), leading to slowing down of retinal circulation, which, in turn, leads to venous stasis, then venous thrombosis. The arterial occlusion also produces ischemic capillaropathy. Restoration of arterial circulation in the presence of venous thrombosis and capillaropathy results in hemorrhagic retinopathy.

An imbalance between the normal intraocular pressure and the blood pressure in the retinal vascular bed—i.e., a high intraocular pressure and a fall of the blood pressure—would produce venous stasis and ischemia. This may be responsible for the frequent association of central retinal vascular occlusion with glaucoma.

## Summary

Fluorescence fundus angiographic and experimental studies indicate that the hemorrhagic retinopathy seen in occlusive vascular disorders is due to a combined occlusion of the central retinal artery and vein and is not due to venous occlusion; the latter produces no retinal damage. Inability to demonstrate an arterial block, using fluorescence fundus angiography, in cases with central retinal artery or arteriovenous occlusion, does not mean that the artery was not previously blocked. The term "central retinal vascular occlusion" is suggested to replace "central retinal venous occlusion."

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# NOTES, CASES, INSTRUMENTS

## DISPOSABLE KERATOME BLADE AND ITS USE IN CATARACT SURGERY

J. Elliott Blaydes, Jr., M.D.
*Bluefield, West Virginia*

Keratomes developed subsequent to the Daviel keratome have undergone wide modification.[1,2] I designed a new and disposable keratome* in order to provide better control of the size of the incision, to eliminate beveling and injuries to the iris and lens capsule, and dulling of the blade.

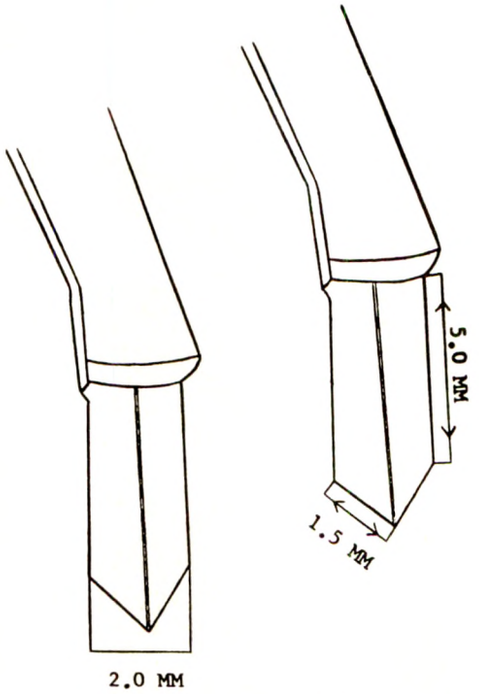



Fig. 1 (Blaydes). New disposable keratome blade.

From the Blaydes Eye Foundation, Bluefield, West Virginia.
Reprint requests to J. Elliott Blaydes, Jr., M.D., 107 Federal Street, Bluefield, West Virginia.
* Available from Rudolph Beaver, Inc., 480 Trapelo Road, Belmont, Massachusetts 02178.

This keratome is made of hard surgical steel and is designed to fit the standard four-inch Beaver chuck handle. The entire blade is 6.5 mm long and 2 mm wide. The leading edge is honed to a tip by the manufacturer, providing two 1.5 mm leading edges ending in a sharp point (Fig. 1). This blade has been used in over 1500 cataract procedures.

I prefer a vertical incision at the 12 o'clock meridian at the posterior one-quarter of the limbus, ending in or near Schwalbe's line; however, other types of incisions are easily carried out with this blade.

### Summary

I have used a disposable keratome in over 1500 cataract extractions. The blade is 2 mm wide, 6.5 mm long, with a 1.5 mm leading edge. The blade is designed to fit the four inch standard Beaver chuck handle.

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## NEEDLE WITH WIRE LOOP FOR DRAWING SUTURES THROUGH TISSUE

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A small, sharp needle has been devised that carries a loop of fine steel wire (Fig. 1). The needle is stainless steel, 7.14 mm

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* Available from Smith, Miller, and Patch, ronto 19, Ontario, Canada.

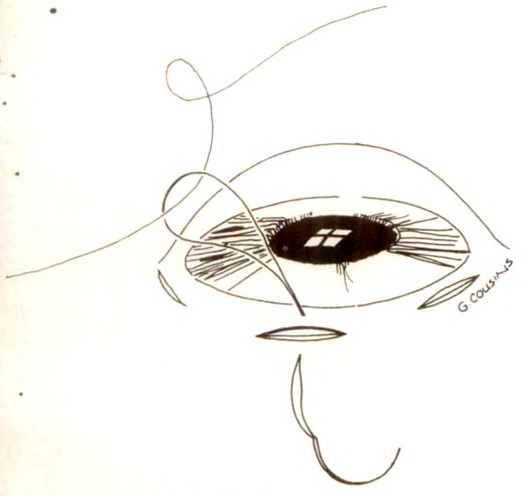


Fig. 1 (McCulloch). Needle with wire loop.

length along the curve, and 0.280 mm in diameter. It is hand-honed, of triangular cross-section, and is reverse cutting. The outside edge of the triangle is rounded except close to the point. The triangle melts to a circle at the base of the needle. The curve of the needle is of 2.38 mm radius, forming an arc of 170 degrees. The wire loop is of stainless steel, fully annealed. It is 32 mm long, and the two ends of the wire are attached to the needle by swaging to its base.

The needle and loop are useful in a number of procedures.[1] Particularly, the loop has value in resolving an emergency during the performance of a penetrating keratoplasty, while using a continuous 9-0 or 10-0 nylon suture. If the surgeon has sewn the nylon suture half or three-quarters of the way around the cornea when the thread breaks, a new suture is usually required. This can be tied to the suture already inserted, leaving an unwanted knot, or the original suture can be removed and the sewing begun afresh. Rather than either poor alternative, the surgeon can continue his sewing, using the wire loop. He merely inserts the free end of the broken, nylon continuous suture through the wire loop and draws the nylon suture through the tissue. This can be done with either end of the broken suture. In this way the surgeon can advance through the remaining steps of the operation, using the original nylon, and without the need of further knots to join broken ends or of removing a length of running suture.

The wire of this loop is very fine and soft. To insert the thread through the loop, the surgeon should use an operating microscope. A sharp instrument is helpful to separate the two sides of the loop, and accuracy is essential to pass a suture through the loop. The loop itself runs easily through the tissues and will draw after it any suture that is likely to be used in microsurgery.


### Summary

A fine, sharp needle that carries a wire loop is described as variously useful in microsurgical procedures, and particularly helpful as an emergency device, permitting the continuation of the single-thread suturing around the cornea when the thread breaks during a penetrating keratoplasty procedure.


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## SCLERAL DEPRESSOR

### Marker for Retinal Detachment Surgery


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The cryosurgical treatment of retinal detachment, utilizing modifications of the Custodis procedure, requires a precise localization of retinal tears. Localization with the cryosurgical probe is a difficult maneuver for


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the inexperienced assistant because no visible lesion remains on the scleral surface after freezing.

Gass[1] introduced a scleral marker in 1966. It resembled the thimble-type scleral depressor with a hollow, stainless steel tube attached to its tip after the cross bar was removed. When applied to the sclera with moderate pressure, a dark, ring-shaped impression remains for 20 seconds. The sclera is then permanently tattooed with a marking pencil. The Gass instrument was found superior to other available markers, but had several disadvantages. Even with rotation of the eye, locating posteriorly positioned tears remains a difficult exercise because the curvature of the instrument prevents its use deep within the bony orbit. The tip of the instrument does not glide smoothly over the scleral surface and is unsatisfactory when dealing with small retinal holes which require scleral indentation and a careful retinal examination prior to marking.

In order to alleviate these two problems, a new instrument was designed which combines a scleral depressor and marker.* The marking portion incorporates the same tip found on the Gass instrument. It is mounted on a flat, straight handle to provide easy access to the posterior sclera without ocular rotation or interference from the orbital rim. Scleral marking of retinal tears is accomplished in the manner described for the Gass design. The smooth, round tip of the opposite end serves as a scleral depressor and avoids tissue damage during the premarking examination.


## Summary

To facilitate scleral marking of retinal tears in surgical treatment of retinal detachments, the Gass scleral marker was mounted on a flat, straight handle. A smooth round tip on the opposite end of the handle serves as a scleral depressor.


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* Available from Storz Instrument Company, St. Louis, Missouri.

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## THE 1971 ACADEMY

The 76th annual meeting of the American Academy of Ophthalmology and Otolaryngology, September 20-24, 1971, at the magnificent convention center of Las Vegas, Nevada, was outstandingly successful. With A. Edward Maumenee as president, over 10,000 members and guests (3,300 ophthalmologists and 1,700 otolaryngologists) registered for an exciting meeting. The convention hall was large enough so one could find a seat for the sessions and not have it disappear if one dared to stand up. Instruction courses were popular and the rooms assigned to them were adequate in size.

The meeting opened September 20th with some 25 members receiving honor awards for their contributions to the scientific programs, continuing education, and the instruction program of the Academy. These awards were followed by a symposium on health science liability moderated by George E. Shambaugh, Jr., of Chicago. One came away from this symposium impressed with the variety of viewpoints expressed by the panelists, with few areas of agreement, as ophthalmologists who were attorneys presented their views, and a plaintiff's lawyer

discussed his. Two otolaryngologists then summarized. Underlying the whole discussion was a patient failure to recognize that less than a perfect result did not constitute irresponsibility or lack of expertise on the part of the physician, and that results could never be guaranteed. Conversely, surgeons appear to feel that some type of "no fault" insurance should be available so that patients who incurred hurt could be compensated without the necessity of litigation. Physicians were strongly opposed to contingency fees, but the plaintiff's attorney held that these provided the poor with expert legal talent they would not have if they were called upon to pay for it. The exchange was stimulating and emphasized the need for continuing study, with particular need for communication between attorneys, physicians, and community leaders.

The guest of honor in ophthalmology was Professor Norman Ashton, who discussed the eye in malignant hypertension. He produced hypertensive retinopathy in monkeys by renal ischemia, and showed, in a beautiful electron microscopic preparation, leakage areas of breaks in the endothelium of precapillary arterioles. He postulated that focal constriction of the arterioles causes muscle degeneration, with the opening of the arteriole and rupture of the endothelium as it is exposed to the full force of the blood pressure. Leakage of plasma and fibrin into and through the damaged blood vessel wall causes intramural deposition of fibrin, providing the histologic picture, of fibrinoid necrosis and retinal exudates. The lecture was magnificently illustrated and delivered with the grace and style we all expect from Professor Ashton.

President Maumenee designated six colleagues as honor guests and their lectures were scattered throughout the program. Joaquin Barraquer of Barcelona presented a beautifully prepared film of management of dislocated lenses. In children, the lens was aspirated through an 18-gauge needle, while the adult lens was extracted through a large incision. David Cogan presented three families with congenital ocular motor apraxia in which the mode of transmission appeared as either an autosomal dominant or an autosomal recessive. He showed striking pictures of the inability of the children to move their eyes voluntarily, giving rise to characteristic jerky head movements when attempting to fix upon a moving object or to read. With labrynthine stimulation by rotation of the head, the eyes moved to extreme positions of gaze.

Michael J. Hogan presented a beautiful example of electron microscopy of the retinal pigment epithelium and choriocapillaris. He related these to changes occurring in macular degeneration. Irving H. Leopold discussed problems in ophthalmic drug therapy, with particular attention to the interaction of drugs, the inborn capacity of an individual to handle drugs, and the systemic effects of topically applied agents. Frank W. Newell discussed the clinical and histologic correlations of drusen and fundus flavemaculatus. Lorenz E. Zimmerman indicated the value of reprocessing paraffin-prepared material for re-examination with the electron microscope. Additionally, he indicated the unusual value of preparing small specimens (such as corneal buttons) immediately for electron microscopy although the tissue is destined for light studies; thus if the tissue proved of unusual interest, good preparations for electron microscopy are possible.

The XXVIII Edward Jackson Memorial Lecture was presented by Enrique S. Malbran of Buenos Aires, Argentina, who provided unique pathologic material of cornea dystrophies studied mainly by means of histochemistry. The lecture was in the grand tradition of the Jackson lecturers, and it will appear in an early issue of the JOURNAL.

Two major symposia were presented. Robert Shaffer moderated one on microsurgery of the outflow channels. The speakers included Doctors Krasnov of Moscow, Dannheim of Germany, Cairns of (Cam-

bridge) England, Spencer of (San Francisco) California, Grant of (Boston) Massachusetts, and Podos of (St. Louis) Missouri. It seemed evident that this type of surgery is most effective in congenital anomalies of the angle and that its value in open-angle glaucoma is not precisely established.

Morton F. Goldberg moderated a symposium on genetics as applied to ophthalmology. Speakers included Doctors David Yi-Yung Hsia, Edward Cotlier, John M. Opitz, and Harold E. Cross. Once again, the key position of the ophthalmologist in recognizing and distinguishing congenital and genetic defects was emphasized. In addition to these presentations, there was an additional 38 papers and films presented with accompanying discussions.

A major change in the direction of the Academy occurred at the annual business meeting. Howard P. House, an otolaryngologist of Los Angeles, was named president to succeed A. Edward Maumenee. Kenneth L. Roper, Chicago, was named president-elect after having served as secretary for ophthalmology for nearly 20 years. He was succeeded as secretary for ophthalmology by Frederick C. Blodi of Iowa City. Edward W. D. Norton of Miami was named first vice-president and Webb Chamberlain of Cleveland, third vice-president. David Shoch of Chicago was named secretary for instruction in ophthalmology, succeeding Glen Gibson of Philadelphia, who served some 17 years in this post and is responsible for establishing the current pattern of instruction courses. Bradley R. Stratsma continues as secretary for continuing education for ophthalmology, an enormous enterprise involving the self-assessment examination and continuing education for residents and members. Clair M. Kos, Iowa City, was re-elected executive secretary-treasurer and Wesley Bradley, Syracuse, an otolaryngologist from Syracuse, New York, was elected councillor.

An enormous number of additional meetings surrounded the main meeting. There were breakfast, lunch, and dinner meetings of innumerable special committees, ophthalmic and otolaryngologic societies and alumni groups. With these meetings combined with the usual scientific program and instruction courses, the conscientious ophthalmologist was involved from breakfast meetings at 7:30 in the morning to the conclusion of a scientific program at 10:30-11:00 o'clock at night. Many ophthalmologists attended the following public gatherings: American Society of Ophthalmic and Otolaryngologic Allergy; Eye Bank Association of America; American Society of Ophthalmic Plastic and Reconstructive Surgery; Ocular Microbiology and Immunology Society; American Society of Ocularists; a contact lens medical seminar; Association for Research in Vision and Ophthalmology, a stimulating program chaired by David Cogan discussing misdiagnosis in neuro-ophthalmology; a joint meeting of the Association of the National Society for the Prevention of Blindness and the Association for Research in Vision and Ophthalmology concerning glaucoma; Ophthalmic Photographers Society; a joint session of the Academy and the committee on drugs and the Association for Research in Ophthalmology and Vision concerning the pathologic effects of light upon the eye; the American College of Veterinary Ophthalmologists; a film program of the International Eye Film Library; a joint meeting of the American Orthoptic Council and the American Association of Certified Orthoptists; the American Association of Ophthalmology public affairs workshop; the Reconstructive and Plastic Surgery in Ophthalmology evening meeting; the scientific meeting of the American Association of Certified Orthoptists.

There were over 21 purely scientific exhibits in ophthalmology, combined with an additional 12 instructional exhibits. For the first time this year, those whose scientific exhibits were winners were awarded beautiful medallions appropriately named the William L. Benedict awards. First award was

for "Fluorescein angiography of the anterior segment," by Pierre M. Amalric, Edward W. D. Norton, Johnny Justice, Jr., and Mizuo Matsui. Second award was for "Time curves of the effect of miotics on intraocular pressure and outflow facility," by Paul C. Barsam, and the bronze award was for "Retinopathy in experimental diabetes," by Ronald L. Engerman, Matthew D. Davis, and James M. B. Bloodworth.

It was a tired group that left the Academy this year convinced of the extraordinary educational impact of this meeting. The next meeting is scheduled for September 24-28 in Dallas, Texas.

Frank W. Newell

## IN MEMORIAM

### Clarence H. Graham

Professor Clarence H. Graham of Columbia University died July 26, 1971, at the age of 65 years. He was renowned for his contributions to visual science and for his training of over 70 recipients of the doctor of philosophy degree.

Dr. Graham received his A.B., M.A., and Ph.D. degrees from Clark University in Worchester. His doctoral disertation (1930) concerned binocular summation. Thereafter, he collaborated with Dr. R. Granit and later with Dr. H. K. Hartline in the recording of nerve impulses in single cells of Limulus. From 1934 through 1941, he and his students at Brown University used psychophysical techniques to study threshold interactions of intensity, time, and area. During and after World War II, he was interested in space perception. At Columbia in the 1950s, he turned his attention to color vision and, in collaboration with Dr. Yun Hsia, investigated some fundamental characteristics of color blindness. In recent years he turned again to space perception, and he and his students studied movement perception.

Professor Graham was the recipient of many honors and awards including the Warren Medal of the Society of Experimental Psychologists (1941), the Presidential Certificate of Merit (1948), The Tillyer Medal of the Optical Society of America (1963), and the distinguished Scientific Contribution Award at the American Psychological Association (1966). Dr. Graham was elected to the National Academy of Sciences, the American Philosophical Society and the American Academy of Arts and Sciences.

Dr. Graham's living memorial is the many graduate students he trained during his career. His students hold him in respect and affection, exemplified by the fact that they call themselves his "academic family."

Joel Pokorny

## CORRESPONDENCE

### Protective moist dressing

Editor,
American Journal of Ophthalmology:

At the time we submitted our manuscript entitled "Protective moist chamber eye dressing" (Am. J. Ophth. 71:1333, 1971), we were unaware that the method had been previously described by Dr. Stanley Golden, M.D., of Redwood City, California (Am. J. Ophth. 55:384, 1963). We wish to acknowledge his prior report.

Robert W. Hollenhorst
Charles F. MacCarthy

## BOOK REVIEWS

The Endothelium of the Cornea and its Clinical Implications, 2nd ed. By Frederick W. Stocker, Springfield, Charles C Thomas, 1971. Clothbound, 250 pages, table of contents, bibliography, 124 black and white figures. $14.25

This is an important and extremely readable book by a clinician and researcher of great experience and maturity. In this brief work, Dr. Stocker reviews in perspective the enormous literature available on the endo-

thelium, and interprets it with judgment and balance. He summarizes the necessary concepts of endothelial anatomy and physiology in a way that is valuable to both basic scientists and clinicians, and presents in detail many important clinical manifestations of corneal endothelial disease.

In some areas Dr. Stocker could be considered to overly stress his own work and concepts, and in others he emphasizes certain controversial and unproven therapies (e.g., rutin and vitamin A therapy for corneal edema, full thickness lamellar keratoplasty for bullous keratopathy). These areas are minimal, however, and do not spoil the generally well-rounded presentation of an important subject.

This book is highly recommended for students of ophthalmology as well as basic scientists and clinicians.

Herbert E. Kaufman

THE CONTROL OF EYE MOVEMENTS. Edited by Paul Bach-Y-Rita, Carter C. Collins, and Jane E. Hyde. New York, Academic Press, 1971. Clothbound, 560 pages, table of contents, index, 322 black and white figures. $14.50

This book records the proceedings of a symposium held under the auspices of the Smith-Kettlewell Institute of Visual Sciences of the Pacific Medical Center in San Francisco at the time of dedication of a new building of that institute in November, 1969. The purpose of the symposium was to assemble visual scientists and clinicians for an exchange of views on physiological aspects and clinical correlation of eye movement control. Participants included physiologists, pharmacologists, bioengineers, physiologists, and neuro-ophthalmologists. Indeed, the list of contributors reads like a "who's who" in the field of eye movement studies.

The first part of the book deals with physiological aspects of eye movement controls and contains original contributions and comprehensive reviews on the probable role of muscle spindles and tendon organs on the control of eye movements, the pharmacology of extraocular muscles, central oculomotor pathways, vestibular ocular reflexes, and other related subjects. In this section, a paper by Hoyt and Daroff, "Clinical Anatomical and Physiological Correlations of Supranuclear Disorders of Ocular Control Systems in Man," is especially noteworthy. It provides a superb review of the supranuclear ocular motor syndromes and signs in terms of current physiological concepts. It also points up the many opportunities for interdisciplinary investigation of eye movement anomalies.

Perhaps because of the intriguing interdependence between its sensory and motor functions, the visual system has held a great fascination for bioengineers and other scientists engaged in the modeling of system behavior. This is reflected in the second part of this book in which we find the latest (and often brilliant) work on orbital mechanics, the dichotomy of the saccadic and the pursuit movement system, the version and vergence systems, and vestibulo-ocular functions. Undoubtedly, some of this work will eventually have direct clinical implications, whereas other aspects, such as the independence of the saccadic and the pursuit system, provide the experimental basis for what has been clinically observed for the past 50 years.

The most exciting aspect of this book is that it points to numerous possibilities of a fruitful interdisciplinary approach in the study of eye movement anomalies by combining the talents of various types of visual scientists and clinicians. This should not only enhance the efficiency of neuro-ophthalmic diagnosis, but also ultimately lead to better insight into the physiology and pathophysiology of the oculomotor system.

Acquisition of this book is a "must" for anyone interested in the field of normal or abnormal eye movements, and the scientific community is indebted to the organizers of this symposium for making this information available.

Gunter K. von Noorden

VIRUS ET UVEITES. By A Catherine Martenet. Paris, Doin Editeurs, 1971. Paperback, 136 pages, table of contents, bibliography, 27 black and white figures and 11 color figures. 65.00 F.

This short monograph details the biology of viruses which have been implicated in ocular disease. Subsequently, it covers the clinical aspects of viral uveitis with particular emphasis on diagnostic procedures in viral uveitis and cites the author's own experience.

An important section is devoted to experimental viral uveitis together with the presentation of Madam Martenet's experiments in inducing uveitis in rabbits.

A necessarily limited section on therapy of ocular viruses considers the possible theoretical approaches for the future. A valuable bibliography is appended.

Marcel Frenkel

THE SECOND CONFERENCE ON THE CLINICAL DELINEATION OF BIRTH DEFECTS. PART VIII. EYE. Edited by Daniel Bergsma. Baltimore, William and Wilkins, 1971. Clothbound, 213 pages, table of contents, index, 316 black and white figures. $17.00

The second conference on the clinical delineation of birth defects was held at Johns Hopkins Hospital in 1969, and was devoted to the eye. Happily, the volume is dedicated to that gentle scholar, Frank Burton Walsh, who continues his active teaching, research, and consultation.

The book consists of generalized discussions of corneal dystrophies and chorioretinal disorders with additional chapters on Norrie's disease, oculocutaneous albinism, Rieger's syndrome, and microphthalmia. Many of the discussions are devoted to classification and textbook description of the various disorders. The authors are experts with much clinical awareness, and the text is richly illustrated. The book concludes with 23 illustrated case reports.

The text provides interesting information for the ophthalmologist who is involved more and more in the recognition of genetic disorders.

Frank W. Newell

CORRECTION OF SUBNORMAL VISION, 2nd ed. By Norman Bier. New York, Appleton-Century-Crofts, 1970. Clothbound, 287 pages, table of contents, bibliography, index, 170 black and white figures. $14.00

The second edition of this book has been revised and expanded. The section on multifocal systems and magnifiers have each been made into a chapter and a chapter on visual efficiency has been added. The chapters on clinical procedures have been rearranged.

This book merits a place in the library of the ophthalmologist who is particularly interested in the correction of subnormal vision. It contains a fairly complete, if somewhat confusing description of various types of lenses and magnifiers and therefore might serve as a reference.

The chapter on visual efficiency is perhaps the most useful part of the book. Everyone who works with patients with subnormal vision has certain favorite devices which he prescribes under certain circumstances. Mr. Bier gives no hint of which devices have proved most helpful to him. Many clinicians will not approve of the emphasis on telescopic lenses.

Since Mr. Bier is an optometrist, it is not surprising that the sections on clinical procedures and the case reports would seem to be of greater interest to optometrists than to ophthalmologists.

Daniel Snydacker

TEACHING THE VISUALLY LIMITED CHILD. By Virginia E. Bishop. Springfield, Illinois, Charles C Thomas, 1971. Clothbound, 214 pages, table of contents, index, 21 black and white figures. $9.50

This book represents the ideas and theories of the author gained from extensive research and personal experience in working with the visually handicapped. The author's

stated purpose in writing this book is to provide workable ideas for efficient teaching in this field.

The book contains 10 chapters. The first three chapters discuss eye disease and suggested classroom adaptations to meet these handicaps. Included here is a brief chapter on visual perception. Chapters 4 through 6 deal with actual classroom teaching. Objectives and specific activities are outlined for teaching required subject matter and other valuable skills such as typing. These chapters are very good and could be a great aid to the teacher of visually handicapped children. Many suggestions are applicable to the teaching of the normally sighted child as well. Chapters 7 through 10 are excellent sources of information for anyone dealing with the visually limited, most especially those involved in instituting or coordinating special programs for the visually handicapped. These chapters stress Resources, special services, specialized programs and sources of professional assistance available to those interested.

This book does contain, however, a number of inaccuracies in regard to eye disease and the adaptive measures that should be taken in the classroom, e.g., ". . . 18-20 inches reading distance should be encouraged and sensible limits should be set up for the amount of close work required, to avoid eye fatigue in the farsighted child" (page 8). Nor does evidence support the statement that "the farsighted child may be subject to severe headaches and/or nausea during periods of close work" (page 8).

In discussing strabismus, the author has confused suppression with arrested vision, stating that when suppression occurs vision is permanently lost (page 11). Page 25 contains a misinterpretation as to the meaning of 10/200 vision.

The strength of this work lies in the educational content, which is very well done. Perhaps the chapter on visual perception might better have been deleted by the author, however, since the material is of such a controversial nature.

The parts of the book dealing with ophthalmology reflect significant deficiencies which seriously compromise the value of these sections. This appears to be due to lack of sufficient consultation with an ophthalmologist.

This book is well written and can certainly be of value to the teacher entering this field. Any teacher can well benefit from the author's experience and her obvious enthusiasm for teaching the visually handicapped.

Jane Dunn Lavoie

# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ACTA OPHTHALMOLOGICA

ON THE PROGNOSTIC VALUE OF INTRAOCULAR PRESSURE IN TREATMENT OF RETINAL DETACHMENT. Ehlers, N. and Osterby, E. (Arhus Kommunehospital, 800. Arhus C, Denmark), Acta Ophth. 48:181-185, 1970.

Among 102 cases of retinal detachment the intraocular pressure was found to be lower in the detachment eye than in the contralateral eye. No significant difference was found between pressures in the reattached and non-reattached cases. There was a significantly lower frequency of reattachment ($P < 0.05$) among cases with a pressure reduction of more than 2 mm Hg than among the remaining cases of the material. (3 tables, 8 references)—Authors' abstract

LEBER'S DISEASE. Seedorff, T. (Rigshospitalet, University of Copenhagen, Denmark), Acta Ophth. 48:186-213, 1970.

The author studied 20 pedigrees with Leber's optic neuritis. In four of these families there were numerous descendants so that some accuracy was obtainable to evaluate the type of inheritance. Two of the pedigrees were particularly valuable since they had enormous number of descendants. In these two pedigrees, both followed through 8 generations and representing 229 and 116 persons respectively, it was not possible to demonstrate mothers who could be said with certainty to be free of the trait. The results of studying these two pedigrees support the assumption that all women born in the pure female lineage are carriers. This result cannot be disproved by the study of the other 18 pedigrees. Thus the study has demonstrated that a carrier-rate of 100% does occur. It has made probable, but not definitely proven, that this is a general rule. (8 figures, 12 references)—David Shoch

DENDRITIC KERATITIS. II. FOLLOW-UP EXAMINATION OF CORNEAL OPACITY. Norn, M. S. (Kommunehospitalet, Copenhagen, Denmark), Acta Ophth. 48:214-225, 1970.

A series of 109 patients who had had dendritic keratitis (the first attack on the average 13 years previously) have been followed up. Corneal opacity was seen in 85%, most often localized centrally. It was ramified in no more than one-fourth of the cases and covered on an average 10% of the corneal area. Blood-vessel invasion was found in half of the affected eyes. The size of the opacity (area and depth) and the vascularization was seen to become aggravated with increasing length of the observation period, as well as after some relapses, after treatment with steroids, and probably also after IDU treatment. The result of the present investigation suggested that iodine cauterization gives the least opacity. Hudson-Stahli's line was found in 52%, apparently equally often in the different age groups, and more frequently than in a normal series, where the line is a fairly rare phenomenon especially in the young age classes. Signs of previous iritis were seen in 21%. (1 figure, 3 tables, 9 references)—Author's abstract

LOCALIZATION OF BACTERIA ON SINGLE EYELASHES. Norn, M. S. (Kommunehospitalet, Copenhagen, Denmark), Acta Ophth. 48: 237-244, 1970.

A total of 153 single eyelashes epilated from 33 eyes of 17 patients have been subjected to bacteriological examination. Staphylococci were detected in all the patients. . . . Staphylococcus albus were found on 56% and Staphylococcus aureus on 5% of the lashes. . . . Practically all the S. albus strains were susceptible to erythromycin. . . . The bacteria were most often situated in or around the root of the lash, more rarely at the tip. (2 tables, 14 references)—Author's abstract.

FLUORESCEIN ANGIOGRAPHY OF THE OPTIC DISC AND PERIPAPILLARY AREA IN CHRONIC GLAUCOMA. Raitta, C. and Sarmela, T. (Helsinki University Eye Hospital, Finland), Acta Ophth. 48:303-308, 1970.

A fluorescein study of the papillary and peripapillary region in 12 patients with chronic wide angle glaucoma and cupping of the disc is presented. Diminished vascularity of the disc and circumpapillary choroidal atrophy was a constant finding in the series. In advanced glaucoma with severe functional loss a peripapillary atrophic area was typical. Severe vascular changes not only of the disc but of

the juxtapapillary and peripapillary zone indicated that a zonular arrangement of the choriocapillaris might exist. (4 figures, 1 table, 6 references)—Authors' abstract

MEDIASTINOSCOPY WITH LYMPH NODE BIOPSY CARRIED OUT IN PATIENTS WITH ENDOGENOUS UVEITIS OF UNKNOWN ETIOLOGY. Nordentoft, V. and Moller, P. M. (Odense County and City Hospital, Odense, Denmark), Acta Ophth. 48:331-344, 1970.

Of 108 patients with endogenous uveitis, sarcoidosis was found to be the etiological factor in 13%. However, in the bilateral cases sarcoid was the etiologic factor in 20%. Mediastinoscopy was performed in 77 of these patients and in 14 giant cell granuloma was demonstrable. No serious complications followed the mediastinoscopy, which was performed under general anesthesia by the chest surgeons. X-ray of the chest showed definite normal conditions in five of the patients in whom mediastinoscopy with biopsy demonstrated sarcoidosis. (2 figures, 5 tables, 29 references)—David Shoch

DENDRITIC KERATITIS. IV. FOLLOW-UP EXAMINATION OF CORNEAL SENSITIVITY. Norn, M. S. (Kommunehospitalet, Copenhagen, Denmark), Acta Ophth. 48: 383-395, 1970.

A series of 96 patients who had had their first attack of unilateral dendritic keratitis not less than five years previously—on an average 13 years previously—had their corneal sensitivity measured. In 81% the sensitivity was markedly impaired, compared with that of the contralateral eye. The average pressure required for the touching to be recognized was four times higher on the keratitis-affected eye than on the contralateral. In 12% the hypesthetic region was localized centrally, in 14% peripherally, being sector-formed, while in 22% it comprised half of the cornea, and in the remainder it was diffuse. Declining corneal sensitivity was found to be positively correlated to rising number of relapses, presence of opacity, blood-vessel invasion of the cornea, stainability of the cornea, reduced wetting time, defects or absence of Fischer-Schweitzer' fluorescein pattern, previous iritis, and increasing impairment of vision. It is possibly correlated to increasing depth of corneal opacity. The corneal sensitivity seems not to be correlated to the length of the observation period nor to present of Hudson-Stahli's line and hardly to herpes of the lip. Sequelae of dendritic keratitis (opacity, pathological Fischer-Schweitzer's fluorescein pattern, impaired sensitivity) were not visible in three of the 96 corneae. (1 figure, 6 tables, 12 references)—Author's abstract

SIDE EFFECTS FROM USE OF LONG-ACTING CHOLINESTERASE INHIBITORS IN YOUNG PERSONS. Axelsson, U. and Nyman, K. (Sabbatsberg Hospital, Stockholm, Sweden), Acta Ophth. 48:396-400, 1970.

A group of 18 young persons with various types of accommodative convergent deviations and treated with Fluropryl or Phospholine Iodide, was studied with regard to side effects. Transient lens clouding was observed in two cases and iris cysts appeared in seven patients. On re-examination six to ten months after discontinuance of treatment iris cysts persisted in three patients and in two, a patchy depigmentation of the pipillary border and the surrounding iris was observed. (4 references)—Authors' abstract

PSEUDOEXFOLIATION OF THE LENS CAPSULE. III. OCULAR TENSION IN EYES WITH PSEUDOEXFOLIATION. Hansen, E. and Sellevold, O. J. (Namdal Hospital, Namsos, Norway), Acta Ophth. 48:446-454, 1970.

In 65 men and 177 women with unilateral pseudoexfoliation and otherwise normal eyes, a significantly higher level of tension was found in eyes with pseudoexfoliation compared with those in which this condition was not present. The average difference in which this condition was not present. The average difference in tension was 2.15 mm Hg in the men and 1.46 mm in the women. In 59 men and 88 women with bilateral pseudoexfoliation but otherwise normal eyes, the average difference in tension between the two eyes was much less. There were significantly more patients with unilateral pseudoexfoliation in whom tension in the eye with pseudoexfoliation was clearly higher than in the other eye than there were patients in the group with bilateral pseudoexfoliation in whom a clear difference in tension between the two eyes was observed. In a group of patients with unilateral pseudoexfoliation who had not developed glaucoma during the period of observation, a record was kept of deviations in the ocular tension over a number

of years. No tendency for the ocular tension to increase in eyes with pseudoexfoliation was observed. Findings indicate that the essential changes which affect ocular tension take place during an early phase of the exfoliation process. (3 figures, 1 table, 1 reference)—Authors' abstract

ORBITAL PNEUMOTOMOGRAPHY. Bertelsen, T. I. (University of Bergen, Bergen, Norway), Acta Ophth. 48:616-624, 1970.

Seventeen patients with primary tumors of the orbit were examined by pneumotomography. This method gives the best results in benign, encapsulated tumors where the air can spread over the tumor surface. Tumors of the optic nerve seem to be the growth which is most easily demonstrated. (7 figures, 6 references)—Author's abstract

LONG-TERM PROGNOSIS IN MALIGNANT EXOPHTHALMOS. Riise, R. (Kommunehospilet, Copenhagen, Denmark), Acta Ophth. 48:634-643, 1970.

Ten patients with severe symptoms were followed for 5 to 15 years. The author concludes the disease is self-limited. After periods of months or years, some remission may occur, followed by a stationary stage, characterized by exophthalmos and disturbances of motility. During critical phases, brief treatment with large doses of steroids is recommended. (2 tables, 32 references)—Author's abstract

OPHTHALMODYNAMOMETRY IN APOPLECTIC PATIENTS WITH HEMISPHERICAL INFARCTION OR TRANSITORY HEMISPHERICAL SYMPTOMS. Kjer, P., Eiken, M. and von Wowern, F. (Gentofte Hospital, Copenhagen, Denmark), Acta Ophth. 48:700-709, 1970.

The results of ophthalmodynamometry and carotid angiography are compared in 123 apoplectic patients with hemispherical infarction or transitory hemispherical symptoms. Ophthalmodynamometry showed a significant difference between the two sides in half of the patients with severe stenosis of the carotid artery and in about two-thirds of the patients with carotid occlusion. (5 tables, 18 references)—Authors' abstract

CAROTID-CAVERNOUS FISTULAE. A STUDY OF 18 CASES. Madsen, P. H. (Arhus Kommunehospital and Amts og Bys Sygehus, Denmark), Acta Ophth. 48:731-751, 1970.

A study on a series of 18 patients with carotid-cavernous fistula is presented. Of the cases, 16 were of traumatic origin, while two were of spontaneous onset. . . . Thirteen patients were treated with ligation of the carotid vessels, and two with ligation and muscle emvolization. Lasting effect on the pulsating exophthalmos was obtained in 11 patients; in two the effect was incomplete in spite of repeated operations. . . . Owing to the numerous possibilities of anastomoses, ligation of vessels had to be repeated in five cases in order to obtain an acceptable result. Accordingly, it is desirable to perform a direct operation on the fistula at once. (8 figures, 2 tables, 36 references)—Author's abstract

DIFFERENTIATION OF PAPILLEDEMA FROM PSEUDO-PAPILLEDEMA BY FLUORESCEIN OPHTHALMOSCOPY. Bynke, H. G. and Aberg, L. (University Hospital, Lund, Sweden), Acta Ophth. 48:752-758, 1970.

In 16 cases with papilledema and nine with pseudo-papilledema the optic discs were studied by blue filter ophthalmoscopy after intravenous injection of fluorescein. The deep disc fluorescence was found to be much more marked in the majority of the cases with edema than in the cases with pseudo-edema. However, in four cases with edema it was faint and of the same order of size as in some cases with pseudo-edema. It was concluded that fluorescein ophthalmoscopy is valuable for a differentiation of the two conditions but that the method is not entirely reliable. (1 table, 8 references)—Authors' abstract

CORNEAL SENSITIVITY BY LOW TEMPERATURES. Kolstad, A. (University of Oslo, Norway), Acta Ophth. 48:789-793, 1970.

Exposure to ambient temperatures common in Norway during the winter is found to decrease the corneal sensitivity as measured by an esthesiometer. It is thought that this may explain the higher tolerance to contact lenses experienced during the cold season. (12 references)—Author's abstract

VARIABILITY OF THE ELECTRO-OCULOGRAM (EOG). Van Lith, G. H. M. and Balik, J. (Medical Faculty, Rotterdam), Acta Ophth. 48:1091-1096, 1970.

Variability of the EOG has been determined by making ten EOGs in each of 15 normal subjects. The mean value and standard deviation of the experiments was respectively 2.15 and 0.25. From the results two conclusions have been drawn. Firstly, values lower than 0.25 in the same person has particular meaning. (4 figures, 1 table, 8 references)—Authors' abstract

MESODERMAL DYSGENESIS OF THE CORNEA AND IRIS (RIEGER'S ANOMALY). Zetterstrom, B. (Karolinska Sjukhuset, Stockholm, Sweden), Acta Ophth. 48:1102-1106, 1970.

A case of mesodermal dysgenesis of the cornea and iris is reported in which the anomaly was suspected in the first week of life, its presence being confirmed in the seventh month, and the clinical course of the condition has been followed up for four years at the time of writing. Interesting features of the case were that the bilateral congenital opacity cleared sufficiently for details of the anterior chamber to be photographed and that there was objective evidence of improvement of vision. (5 figures, 7 references)—Author's abstract

BILATERAL HOMONYMOUS HEMIANOPSIA FOLLOWING VENTRICULOGRAPHY. Rasmussen, K. E. (Arhus Kommunehospital, Arhus, Denmark), Acta Ophth. 48:1174-1184, 1970.

Eight cases of bilateral homonymous hemianopsia were found following ventriculography on a material of 335 patients. In five of these cases the vision returned to normal in less than 10 days, in one it had been restored at follow-up six months later, while in two cases no improvement had occurred at discharge from the hospital one and two months after the ventriculography. (12 references)—Author's abstract

THE VALUE OF OCULAR FINDINGS IN THE DIAGNOSIS OF ANGIOKERATOMA CORPORIS DIFFUSUM (FABRY'S DISEASE). Lou Christensen, H. V., Heidensleben, E. and Larsen, H. (Kovwnhavns Amts Syeghus i Gentofte, Denmark), Acta Ophth. 48: 1185-1194, 1970.

In this study of Fabry's disease, 11 out of 15 members of one family presented symptoms and signs of this disorder. It is pointed out that corneal opacities are of great diagnostic value in both heterozygote females and young males presenting only slight general manifestations. The presence of marked focal varicosities and ampulliform or saccular dilatations of the conjunctival vessels together with tortuosity of the vessels may also be of great diagnostic value in this disease. Retinal vascular tortuosity is considered to be of no diagnostic value if not present together with other manifestations of the disease. (6 figures, 1 table, 21 references)—Authors' abstract

DEMODEX, FOLLICULORUM. INCIDENCE AND POSSIBLE PATHOGENIC ROLE IN THE HUMAN EYELID. Norn, M. S. (Kommunehospitalet, DK-1399, Copenhagen K, Denmark), Acta Ophth. Suppl. 108:1-85, 1970.

On the basis of examination of 400 patients the author comes to the following conclusions. Demodex can be found in about 50% of all patients. However, the author does not feel that Demodex folliculorum is the cause of blepharitis. A cylindric formation around the base of the lash suggests presence of Demodex. The cylinder (cuff, collaring around the ciliary root) is an epithelial proliferation of the hair follicle, presumably caused by Demodex movements and metabolic waste products in the follicle. Demodex play a role in the ecology of the skin. The mite can spread S. albus from one hair follicle to another. Demodex can be demonstrated in nearly all people, aged over 70 years. The incidence rises with increasing age. The mite is also found in the younger age classes (e.g. in about 25% of teenagers). (21 figures, 11 tables, 52 references)—Author's abstract

A CLINICAL STUDY OF THE NORMAL HUMAN CENTRAL CORNEAL THICKNESS. Hansen, F. K. (Kommunehospitalet, University of Arhus, 8000 Arhus C., Denmark), Acta Ophth. 49:82-89, 1971.

Central corneal thickness was measured in 150 normal eyes with the Haag-Streit pachometer. A mean value of 0.520 ± 0.018 was found in 76 right eyes, whereas the value of 74 left eyes was 0.004 mm higher due to the angle kappa. A normal frequency distribution is demonstrated. Central corneal thickness is found to increase significantly with increasing intraocular pressure within normal range, and possible to decrease with increasing body height. No correlation between age, refraction and anterior corneal curvature was found. No

sex difference was found. (2 figures, 4 tables, 12 references)—Author's abstract

HUMAN RETINAL VASCULAR OBSTRUCTIONS. Nilsson, S. E. (Karolinska Sjukhuset, 10401 Stockholm 60, Sweden), Acta Ophth. 49:111-133, 1971.

The author examined six patients with central retinal vein obstructions and four patients with central retinal artery obstructions with fluorescein angiography and electroretinography. They found that both these modalities were useful prognostic indicators. Generally in those patients who recovered vision the b waves remained normal while in those who went on to suffer deprivation of vision there was a markedly reduced b wave. Further, the mean retina circulation time for cases with return of vision was 4.2 seconds (as against a normal of 2.2 seconds) while in those cases where the vision did not return the mean retinal circulation time ranged from 7 to 330 seconds. (14 figures, 3 tables, 33 references)—David Shoch

IRIDENCLEISIS. Tarkkanen, A. and Eskelin, L. (Helsinki University Eye Hospital, Finland), Acta Ophth. 49:143-150, 1971.

Iridencleisis was performed on 124 eyes over a five year period. Tensions were controlled in 89% but visual deterioration took place in 23% of these. Persistent hypotony developed in 10%. (6 tables, 12 references)—David Shoch

MODIFIED GONIOPUNCTURE IN THE TREATMENT OF CONGENITAL GLAUCOMA. Vannas, S. and Pohjola, S. (Helsinki University Eye Hospital, Finland), Acta Ophth. 49: 159-164, 1971.

Good ocular tension control was obtained by means of modified goniopuncture in nine eyes of 13, and there were no postoperative complications in these cases. In two eyes a spontaneous cure occurred. Goniopuncture can be recommended as the primary operation in the treatment of congenital glaucoma because of the slight risk of complications and the encouraging results obtained. In addition it should be taken into account that goniopuncture does not preclude a subsequent goniotomy or trabeculotomy, should it prove necessary. (2 tables, 10 references)—Authors' abstract

THE FREQUENCY OF FIBRILLOPATHIA EPITHELIOCAPSULARIS (SO-CALLED SENILE EXFOLIATION) IN PATIENTS WITH OPEN-ANGLE GLAUCOMA. Aasved, H. (University of Bergen, Norway), Acta Ophth. 49: 194-210, 1971.

A total of 444 patients with open-angle glaucoma has been examined to determine the incidence of pseudoexfoliation. The most important factor appears to be the severity of glaucoma. The frequency was considerably higher among patients with optic nerve damage than among patients with normal optic discs and visual fields. Different patient groups collected from the same geographical area but with varying degrees of severity showed an increasing frequency of fibrillopathy in the same sequence as the serverity. . . . These findings seem to concur well with the clinical experience that capsular glaucoma is a more serious condition than ordinary simple glaucoma. Among patients with open-angle glaucoma in Norway as a whole it is assumed that the frequency of fibrillopathy is in the range of 20 to 30% and thus probably not higher than in other countries. (7 tables, 42 references)—Author's abstract

SYNKINESIS OF UPPER LID ELEVATION OCCURRING IN HORIZONTAL EYE MOVEMENTS. Ticho, U. (Hadassah Medical Center, Jerusalem, Israel), Acta Ophth. 49:232-238, 1971.

The motility of the upper eyelid was investigated in 133 subjects with normal eye motility during horizontal movements of the eyes. Elevation was found to be present in abduction in 49% of the cases, in adduction in 15% and during both abduction and adduction it occurred in 14%. . . . Six cases with abducens palsy and three cases with Duane's syndrome presented exaggerated elevation of the eyelid in abduction. The presence of physiologic synkinesis between the lid elevators and the horizontal muscles of the eye is suggested. In cases of 6th nerve palsy and Duane's syndrome the exaggerated nerve impulses to the levator palpebrae muscle could be the cause for the exaggerated lid retraction on abduction. (8 figures, 2 tables, 8 references)—Author's abstract

THE SAGITTAL GROWTH OF THE EYE. I. ULTRASONIC MEASUREMENT OF THE DEPTH OF THE ANTERIOR CHAMBER FROM BIRTH TO PUBERTY. Larsen, J. S. (University of

Bergen, Norway), Acta Ophth. 49:239-262, 1971.

Ultrasonographic measurements of the depth of the anterior chamber were carried out in 80 full-term newborns (43 boys and 37 girls) and in 465 boys and 381 girls aged 6 months to 13 years. Both eyes were measured in all subjects. From birth to the age of 13 the mean value of the anterior chamber depth increased from 2.37 to 3.70 mm for boys and from 2.39 to 3.62 mm for girls, having then reached the same value as in young adults (20 to 40 years). It therefore appears that the increase in the depth of the anterior chamber terminates at the age of 13, or is minimal after this age. The increase in the depth of the anterior chamber takes place in three growth phases: a rapid postnatal phase from birth to the age of one and a half years, with an increase of approximately 0.9 to 1.0 mm, a slower infantile phase from 1 to 7 years with an increase of 0.3 to 0.4 mm and a slow juvenile phase from 8 to 13 years with an increase of barely 0.1 mm. During the whole of the growth period there appears to be a real sex-determined difference in the depth of the anterior chamber of about 0.1 mm, the deepest anterior chamber being found in boys. A negative correlation between the depth of the anterior chamber and refraction develops at an early stage of the growth period, and has in this study been found to be established from the second year of life. (7 figures, 9 tables, 48 references)—Author's abstract

LATE RESULTS OF SURGERY ON EYES WITH PRIMARY GLAUCOMA AND CATARACT. Laatikainen, L. (University of Helsinki, Finland), Acta Ophth. 49:281-292, 1971.

The effect of lens extraction on intraocular pressure in glaucomatous eyes was studied. The material comprised 98 glaucomatous eyes operated on for cataract in the years 1960 to 1968 in the University Eye Clinic, Helsinki. In cases with previous antiglaucomatous surgery, lens extraction had no distinct effect on the intraocular pressure or on the need for antiglaucomatous medication. Only in one eye was loss of filtration found postoperatively. In cases were cataract extraction was the primary procedure, the beneficial effect on glaucoma control was seen in about 70% of eyes with open-angle glaucoma. In 50% of eyes with open-angle glaucoma the pressure was adequately controlled without any postoperative medication. In the more difficult cases of chronic open-angle glaucoma, and in most cases of chronic angle-closure glaucoma, the effect of lens extraction alone seem insufficient to control the glaucoma. (8 tables, 42 references)—Author's abstract

THE FREQUENCY OF RUBEOSIS IRIDIS IN DIABETIC PATIENTS. Ohrt, V. (Aalborg Sygehus, 9000 Denmark), Acta Ophth. 49: 301-307, 1971.

Rubeosis iridis occurs in about 5% of Danish diabetics. . . . As, however, rubeosis is closely connected with proliferative retinopathy, it is more relevant to consider the frequency in this connection and rubeosis was found in 64% of these patients. . . . However, rubeosis is also seen in a smaller number of patients with retinopathy, but without proliferations. Therefore, one arrives at the final conclusion that the frequency of rubeosis in a diabetes material can be considered to be about 60% of the number of the proliferative cases in the series. (5 tables, 13 references)—Author's abstract

## AMERICAN ORTHOPTIC JOURNAL

THE NATURAL COURSE OF ESOTROPIA. Moore, S. (Columbia-Presbyterian Medical Center, New York), Am. Orthoptic J. 21:80-83, 1971.

A child with a moderate degree of esotropia has a 59% chance of his deviation decreasing as he grows up. One out of 10 will become exotropic and neither the change in refractive error nor the presence of amblyopia will influence its development. (3 tables)—Author's abstract

## ARCHIVES OF OPHTHALMOLOGY

AQUEOUS DYNAMICS OF PILOCARPINE-TREATED EYES. THE INFLUENCE OF TOPICALLY APPLIED EPINEPHRINE. Harris, L. S., Mittag, T. W. and Galin, M. A. (New York Medical College, 1249 Fifth Ave., New York), Arch. Ophth. 86:1-4, July, 1971.

Solutions of levoepinephrine borate were prepared in concentrations of 0.6%, 0.12%, 0.25%, 0.50%, 1.00% and 2.00%. These solutions were applied to the right eye only for four to six weeks in a series of open-angle

glaucomatous patients who were receiving 4% pilocarpine to both eyes. Although a small effect was noted with lower doses, no meaningful additional hypotensive response from epinephrine was noted until the concentration reached 0.50%. The maximal additive response occurred with 2.00% levoepinephrine. Although the combined effect of pilocarpine and epinephrine was greater than the maximal effect of either drug alone, it was less than the additive effects of both drugs. Parallelism of the epinephrine and pilocarpine/epinephrine dose-response curves suggests that both drugs act by similar mechanisms. (3 tables, 3 references)—Authors' abstract

THE FIXED DILATED PUPIL. Thompson, H. S., Newsome, D. A. and Loewenfeld, I. E. (University of Iowa, Iowa City), Arch. Ophth. 86:21-27, July, 1971.

Isolated iridoplegia or internal ophthalmoplegia may be due to impairment of the effector muscles in the eye, defective parasympathetic innervation, or the presence of atropinic substances in the eye. Pharmacologic blockade can be identified by the pupil's failure to constrict to pilocarpine drops. Because of its clarity and technical simplicity, this test should be in general use as an office procedure. (6 figures, 12 references)—Authors' abstract

## DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY

VISUAL ACUITY OF A NATIONAL SAMPLE (1958 COHORT) at 7 YEARS. Alberman, E. D., Butler, N. R. and Sheridan, M. D. (National Children's Bureau, 1 Fitzroy Square, London W.1.), Develop. Med. Child. Neurol. 13:9-14, Feb., 1971.

Of 14,197 children at the age of seven, 79% had a visual acuity of 6/6 in both eyes, and in 96% at least one eye had an acuity of 6/9 or better. (5 tables, 6 references)—Joel G. Sacks

## INTERNATIONAL OPHTHALMOLOGY CLINICS

SOME IATROGENIC OCULAR DISEASES FROM SYSTEMATICALLY ADMINISTERED DRUGS. Bernstein, H. N. (Washington Hospital Center, D.C.), Int. Ophth. Clin. 10:553-619, 1970.

An excellent review article that discusses the documented side-effects of various medications. For example, systemically administered steroids have been reported to cause glaucoma, cataracts and papilledema. The antimalarials cause retinal degeneration and keratopathy. The phenothiazine tranquilizers cause retinal degeneration, keratopathy and cataracts. Chloramephenicol has been implicated in optic neuritis as has penicillamine and ethambutol. Triparanol, which is no longer on the market, is known to produce cataracts. These and other drugs are described and the pertinent literature references given. (21 figures, 7 tables, 195 references)—David Shoch

## INVESTIGATIVE OPHTHALMOLOGY

"STEROID-INDUCED" MYDRIASIS AND PTOSIS. Newsome, D. A., Wong, V. G., Cameron, T. P. and Anderson, R. R. (National Institutes of Health, Bethesda, Md.), Invest. Ophth. 10:424-429, June, 1971.

It has been noted clinically that commercial preparations of dexamethasone induce a mydriasis and ptosis. The authors used the usual commercial preparation available (Decadron), the vehicle alone and a solution of dexamethasone in saline to evaluate the relative importance of each constituent. When either Decadron or the vehicle was used to irrigate the anterior chamber of rabbits, mydriasis resulted. No pupil changes were observed after perfusion with dexamethasone in saline. Similarly perfusion with Decadron or the vehicle mixture produced marked to moderate ptosis. However the use of dexamethasone in saline did not cause any ptosis. Therefore, the mydriasis and ptosis reported from the use of steroids appears to be caused by a direct myopathic effect of the vehicle. (3 figures, 1 table, 9 references)—David Shoch

FURTHER STUDIES SUPPORTING THE IDENTITY OF CONGENITAL TRITANOPIA AND HEREDITARY DOMINANT OPTIC ATROPHY. Krill, A. E., Smith, V. C. and Pokorny, J. (Eye Research Laboratories, University of Chicago, Illinois), Invest. Ophth. 10:457-465, June, 1971.

Dominant inherited optic atrophy is usually a stationary disorder with typical findings of temporal optic nerve pallor, abnormal distance acuity, minimal visual-field defects, and char-

acteristic color confusions in the blue-green region of the spectrum. Variability in the severity of these abnormalities is common, even within the same family. In patients with minimal disease, distance acuity may be close to normal and optic pallor may be so subtle that a definitive diagnosis cannot be made unless other obviously affected members of a family are seen. Our studies indicate that patients with dominantly inherited optic atrophy have similar color vision to that previously reported for subjects with congenital tritan defects. In fact, the almost identical color-vision profiles and pattern of inheritance of the two conditions lead us to question the existence of congenital tritan defect as an independent entity. Criteria are suggested for distinguishing the two conditions. It is emphasized that the utmost care should be taken to rule out dominant optic atrophy in future subjects in whom congenital tritanopia is suspected, both because of the strikingly similar characteristics of the two conditions, if these are indeed separate entities, and because the diagnosis of hereditary dominant atrophy may be easily missed. (4 figures, 29 references)—Authors' abstract

RETINAL COLLATERAL VESSEL FORMATION. Klein, R., Klein, B., Henkind, P. and Bellhorn, R. (Albert Einstein College of Medicine, Bronx, New York), Invest. Ophth. 10:471-480, July, 1971.

Retinal vessels of 18 adult domestic cats were successfully embolized with graded glass microspheres, and the resultant vascular changes were monitored clinically by ophthalmoscopy. . . . While collaterals were ophthalmoscopically evident within 24 hours of occlusion, none were identified histologically until seven days after occlusion. These collaterals developed from the pre-existing retinal capillary bed and often attained the same caliber as the occluded vessel. (7 figures, 2 tables, 10 references)—Authors' abstract

CHARACTERIZATION AND INHIBITION OF CORNEAL COLLAGENASE. Hook, C. W., Brown, S. I., Iwanij, W. and Nakanishi, I. (New York Hospital-Cornell University Medical College, 525 E. 68th St., New York, N.Y.), Invest. Ophth. 10:496-503, July, 1971.

This investigation shows that corneal collagenase operates optimally at a physiologic pH and not at 4.0 or above 8.4, and that the enzyme cleaves the collagen molecule into ¾ and ¼ length fragments. Studies on the dynamics of collagenase inhibition show that the enzyme is calcium dependent. Many potential inhibitors were tested. The collagenase inhibitors sodium and calcium ethylenediaminetetraacetic acid (EDTA) probably inhibit collagenase by removing the essential calcium. They were found to be completely reversible. The inhibition of corneal collagenase by cysteine was partially reversible by the addition of calcium, indicating that part of its inhibition is due to chelating. However, more than 50% of cysteine's inhibition is irreversible. Dithiothreitol was also found to inhibit collagenase. Iodoacetate was added to dithiothreitol to alkylate in sulfhydryl groups, and then it did not inhibit collagenase. These results indicate that in addition to inhibiting by chelating calcium, cysteine irreversibly inhibits by reducing a disulfide bond in the enzyme molecule. Finally, guanidinium-extracted corneal proteoglycan was shown to prevent collagenase from breaking down collagen. (4 figures, 5 tables, 21 references)—Authors' abstract

MECHANISM OF DEVELOPMENT OF HEREDITARY CATARACT IN MICE. Iwata, S. and Kinoshita, J. H. (Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, Mass. 02114), Invest. Ophth. 10:504-512, July, 1971.

The biochemical evidence regarding a recessively transmitted cataractous trait in mice suggests that an apparent deficiency of Na-K ATPase may be involved in the initiation of this type of cataract. The enzyme defect leads to inefficiency of the cation pump mechanism. This abnormality was demonstrable in 13-day-old mice. At this stage the lens was clear and the electrolyte levels were normal. However, by the twentieth day it became apparent that the defective lens was no longer able to extrude sodium efficiently, therefore sodium content increased. The sudden increase in electrolytes drew water into the lens and an osmotic change occurred. These events preceded the appearance of a "pin-head" nuclear opacity. (8 figures, 17 references)—Authors' abstract

STUDIES OF AQUEOUS HUMOR DYNAMICS IN MAN. II. MEASUREMENTS IN YOUNG NORMAL SUBJECTS USING ACETAZOLAMIDE AND L-EPINEPHRINE. Kupfer, C., Gaasterland,

D. and Ross, K. (National Institutes of Health, Bethesda, Md.), Invest. Ophth. 10:523-533, July, 1971.

The short-term effects on aqueous humor flow dynamics of single doses of acetazolamide and L-epinephrine, alone and combined were studied in selected young, normal men. Analysis of aqueous flow before and after medication was facilitated by graphic representation of flow versus intraocular pressure, the flow curve. Acetazolamide reduced intraocular pressure and $P_k$ of Goldmann without affecting true facility or pseudofacility. A pattern of pressure-independent reduction of flow occurred. L.-epinephrine reduced intraocular pressure and pseudofacility. A pattern of pressure-dependent change of aqueous flow occurred with reduction of flow at intraocular pressures below approximately 30 mm Hg. When acetazolamide was combined with epinephrine, additive effects were noted, with an additional decrease of intraocular pressure associated with significant increase of true facility. No change of true facility occurred after epinephrine or acetazolamide alone in these subjects. (5 figures, 8 tables, 16 references)—Authors' abstract

## Johns Hopkins Medical Journal

TEACHING OPHTHALMOLOGY TODAY AND TOMORROW. Paton, D. (Dept. of Ophthalmology, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77025), Johns Hopkins Med. J. 128:208-233, Apr., 1971.

There is an urgent need in ophthalmology to increase the efficiency and effectiveness of teaching.

Lectures that are repeated frequently should be available as single-concept, audio visual recordings so that their repeated delivery will not lessen the effectiveness and stifle the enthusiasm of the lecturer. The simultaneous use of three slide projectors along with the use of a "guest lecturer" from another department is highly successful. Training can be made more efficient with the use of such aids as model eyes, enucleated animal eyes for teaching surgery and movie films. (8 figures, 31 references)—Joel G. Sacks

## Journal of Neurology, Neurosurgery and Psychiatry

CLINICAL SPECTRUM OF OCULAR BOBBING. Susac, J. O., Hoyt, W. F., Daroff, R. B. and Lawrence, W. (Letterman General Hospital, San Francisco), J. Neurol. Neurosurg. Psychiat. 33:771-775, 1970.

Ocular bobbing is a distinctive movement disorder occurring in a variety of related forms herein classified as "typical," "monocular," and "atypical." "Typical" ocular bobbing occurs in patients with paralysis of horizontal conjugate eye movements and consists of abrupt, spontaneous downward jerks of the eyes with a slow return to the mid position. The "monocular" type reflects co-existing unilateral third nerve paresis in addition to the bobbing. The "atypical" type includes either a variation unexplained by associated oculomotor palsy, or bobbing with intact spontaneous or reflex horizontal eye movements. The clinical spectrum of ocular bobbing, its varied causes, and its prognostic significance are exemplified in a report of nine cases. (1 table, 14 references)—Authors' abstract

## Klinische Monatsblätter für Augenheilkunde

PHOTOCOAGULATION IN RETINAL PERIPHLEBITIS. (German) Lemke, L. and Jutte, A. (Univ.-Augenklinik Jena), Klin. Mbl. Augenh. 158:8-15, Jan. 1971.

Twenty patients with a retinal periphlebitis of the haemorrhagic type were treated by photocoagulation, the vascular defects being identified as prestages of haemorrhages in the fluorescence-angiogram. The disease could be brought to a standstill in 18 cases. Under fluorescence-angiographic control, the relapse-free observation period lasted for 1 to 5 years, on the average to 3 years. (2 figures, 1 table, 10 references)—Authors' abstract

SYNDROME OF DANCING EYES WITH MYOCLONIC ATAXIA. (German) Brune, G., Hertel, G. and Gruninger, W. (Univ.-Klinik Wurzburg), Klin. Mbl. Augenh. 158:41-48, Jan., 1971.

A case of dancing eyes with myoclonic ataxia is reported. The syndrome appeared after ex-

posure to infection, showed sudden onset and protracted course. A viral infection or immunopathological mechanisms are suggested to play a role in the pathogenesis of the disease. In addition, it is assumed that irritative lesions within the cerebellar vermis and the brainstem represent the pathomorphological base of the clinical symptomatology. (2 figures, 9 references)—Authors' abstract

ELECTRORETINOGRAPHY, A METHOD OF EXAMINATION TO DETERMINE THE PROGNOSIS IN JUVENILE DEGENERATION OF THE MACULA. (German) Hammerstein, W. (Univ.-Augenklinik, Dusseldorf), Klin. Mbl. Augenh. 158:72-75, Jan., 1971.

While the early stage of a juvenile degeneration of the macula (son) showed a degeneration process which was still restricted to the macula region, the subnormal ERG already indicated a progression of the disease. After a course for decades (father) a degeneration of the entire central area of the retina was seen ophthalmoscopically, with a disappearance of the electroretinal potential. In the initial stage the electroretinogram already gave information on the prognosis of the disease. (4 figures, 12 references)—Author's abstract

TREATMENT OF PROLIFERATING DIABETIC RETINOPATHY WITH DIATHERMY-COAGULATION. (German) Wessing, A. and Bockenhoff, I. (Augenklinik am Klinikum Essen der Ruhruniversitat Bochum), Klin. Mbl. Augenh. 158:212-220, Feb., 1971.

The results are obtained by the examination of 92 treated eyes. In approximately half of the cases diathermy-coagulation results in the arresting of intravitreal proliferation of vessels. Furthermore, diathermy leads to a very rapid absorption of massive hemorrhages in the vitreous body. (1 figure, 3 tables, 23 references)—Authors' abstract

CLINICAL CONSIDERATIONS AND INHERITANCE OF VITELLIFORM DEGENERATION OF THE MACULA. (German) Thiel, H. J. and Behnke, H. (Univ.Augenklinik, Kiel), Klin. Mbl. Augenh. 158:235-246, Feb., 1971.

In three family branches with vitelliform degeneration of the macula, with a total of 565 genealogically related persons, 98 members of the family were available for ophthalmological examination. The disease is transmitted dominant autosomally. Cysts were found and particularly in older persons, scarred stages. (13 figures, 40 references)—Authors' abstract

THE RIGHT-LEFT PROBLEM OF RETINAL TEARS. (German) Jager, A. (51 Aachen, Goethestr. 27/29, Augenklinik), Klin. Mbl. Augenh. 158:272-273, Feb., 1971.

A statistical comparison between patients in one German and three Persian eye hospitals has shown that retinal tears, independently of the direction of reading—in German from left to right and from right to left in the Arabic script—appear more frequently in right eyes than in left eyes. (2 references)—Author's abstract

INITIAL CLINICAL EXPERIENCE OF TREATMENT WITH ADHESIVES IN OPHTHALMIC SURGERY. (German) Muller-Jensen, K. (Augenklinik der Universitat München, Germany), Klin. Mbl. Augenh. 158:573-577, Apr., 1971.

The tissue adhesive butylcyanoacrylate was used in man in three cases of perforating injuries of the cornea and in ten cases of corneal incision for cataract, following extensive animal experiments. Small, smooth perforations of the cornea or incisions by lancet adhered without difficulty. When larger wounds of the cornea or corneal incisions for cataract were treated with the adhesive, it was frequently necessary to use additional sutures for adaptation. The strong adhesion of the adhesive material to the suture may then cause delay for several weeks until the adhesive membrane has been shed spontaneously. This in turn may produce severe keratitic reactions. In lacerated corneal injuries the monomeric adhesive easily enters the wound clefts and polymerises in the parenchyma of cornea. Disorders of wound healing resulted and toxic kerato-iritis with vascular infiltration into the cornea occurred. Altogether the usefulness of adhesive substances in corneal surgery is limited. (3 figures, 4 references)—Author's abstract

ON THE IMPORTANCE OF BLOOD FACTORS IN KERATOPLASTY. (German) Meyer, H. J. (Univ.-Augenklinik Gottingen), Klin. Mbl. Augenh. 158:780-785, June, 1971.

The author studied 250 keratoplasties and subdivided the patients into various prognostic

groups. No dependence of healing on blood factors of the corneal donor could be demonstrated in any group. (5 figures, 1 table, 16 references)—David Shoch

## Scientific American

EYE MOVEMENTS AND VISUAL PERCEPTION. Noton, D. and Stark, L. (University of Colorado), Sci. Amer. 224:35-43, June, 1971.

Angles and other informative details are the features selected by the brain for remembering and recognizing an object. It is hypothesized that as a subject views an object for the first time and becomes familiar with it he scans it with his eyes and develops a scan path for it. During this time he lays down the memory traces of the feature ring, which records both the sensory activity and the motor activity. When he subsequently encounters the same object again, he recognizes it by matching it with the feature ring, which is its internal representation in his memory. (12 figures)—Joel G. Sacks

## Transactions of the American Academy of Ophthalmology and Otolaryngology

OCULAR FINDINGS FOLLOWING RADICAL MAXILLECTOMY. Wilder, L. W., Beyer, C. K., Smith, B. and Conley, J. J. (New York), Tr. Am. Acad. Ophth. Otolaryng. 75:797-801, July-Aug., 1971.

Malignant tumors of the nasopharynx and paranasal sinuses are frequently present with epiphora as the primary complaint. Following radical maxillectomy, ocular ptosis and enophthalmos are common results. Visual acuity and binocular visual function are not often affected. Despite the partial removal of the nasolacrimal duct, dacryocystorhinostomy is seldom necessary. (4 figures, 1 table, 2 references)—Authors' abstract

ORBITAL FLOOR FRACTURES: FOLLOW-UP OF CASES WITH AND WITHOUT SURGICAL REPAIR. Emery, J. M., von Noorden, G. K. and Schlernitzauer, D. A. (Wilmer Institute, Johns Hopkins Hospital, Baltimore), Tr. Am. Acad. Ophth. Otolaryng. 75:802-812, July-Aug., 1971.

Hypocycloidal polytomography appeared to be the most accurate roentgenographic technique currently available for the diagnosis of orbital floor fractures. An analysis of patients who were operated on for orbital floor fractures and were followed for an average period of 3.4 years revealed that 24 of 49 patients had persistent diplopia despite surgical repair. Patients who were operated on within the first week after injury had late diplopia just as frequently as those who were operated on during the second week after injury. A follow-up examination of 18 patients with roentgenographically proved orbital floor fractures which were not operated on revealed that in a significant number diplopia would disappear permanently within two weeks after injury even when surgery was not performed. Thus, patients with orbital floor fractures, who initially either have no diplopia or who lose the diplopia within 14 days after injury should not undergo surgery unless roentgenograms show evidence of an extensive defect of the orbital floor that may cause enophthalmitis if left untreated. (3 figures, 8 tables, 28 references)—Authors' abstract

VITRECTOMY: A PARS PLANA APPROACH. Machemer, R., Buettner, H. and Norton, E. W. D. (Bascom Palmer Eye Institute, University of Miami, Florida), Tr. Am. Acad. Ophth. Otolaryng. 75:813-820, July-Aug., 1971.

An instrument has been described which is introduced into the vitreous cavity through the pars plana. Simultaneously, vitreous is destroyed, aspirated, and replaced by a balanced salt solution. The instrument allows the surgeon to eliminate gel-like vitreous of any consistency and also to cut vitreous strands. With the exception of the vitreous base, almost all vitreous can be removed. The action of this vitreous infusion suction cutter in the eye is observed through a fundus contact lens with the operating microscope. The pars plana approach avoids the common complications in the anterior segment involved in the open-sky technique. Long-standing vitreous hemorrhages, vitreous membranes in diabetic retinopathy, complicated detachments with strong vitreous pull and giant retinal tears have been treated successfully with this technique. (6 figures, 12 references)—Authors' abstract

## TRANSACTIONS OF THE AMERICAN OPHTHALMOLOGICAL SOCIETY

CATARACT EXTRACTION AFTER FILTERING PROCEDURES. Regan, E. F. and Day, R. M. (Edward Harkness Eye Institute, Columbia University, New York), Tr. Am. Ophth. Soc. 68:96-104, 1970.

The authors removed cataracts from 70 eyes with filtering blebs at the 12 o'clock position. They made no attempt to avoid the bleb but made their incisions directly through it. They found that in 60 of the 70 cases, ocular tension control was just as good after the surgery as before. In 10 of the cases control ranged from fair to poor after the surgery. Therefore, the authors conclude there is no need to make special incisions for cataract surgery after filtering procedures since in most cases filtration will continue to work after the surgical procedure. (1 table, 19 references)—David Shoch

LONG-TERM COMPLICATIONS OF BETA-RADIATION THERAPY IN OPHTHALMOLOGY. Barrón, A., McDonald, J. E. and Hughes, W. F. (Illinois Eye and Ear Infirmary, Chicago), Tr. Am. Ophth. Soc. 68:113-128, 1970.

After re-examining 71 patients 5 to 21 years following beta radiation therapy for external ocular conditions, it has become evident that the doses used in the early stages of development of this treatment were unnecessarily high and led in many instances to late complications. However, most of these were tolerable, including development of lens vacuoles in the equatorial region of the lens which then usually migrated posteriorly to the subcapsular region. This rarely caused any diminution of vision and the opacities tended to be stationary, perhaps because of the highly localized nature of the irradiation. It would therefore seem reasonable not to discard this mode of therapy in conditions where it is superior to other methods or in conditions where other methods have failed. Reduction of the size of the dose and greater fractionation of doses can be expected to reduce the incidence of late changes caused by radiation. (9 figures, 4 tables, 16 references)—Authors' abstract

MARSUPIALIZATION OF INOPERABLE ORBITAL DERMOIDS. Kennedy, R. E. (University of Rochester School of Medicine, Rochester, New York), Tr. Am. Ophth. Soc. 68:146-164, 1970.

The best management of deep orbital dermoids is complete surgical removal. If this can not be accomplished without damage to the orbital contents, partial removal is indicated with or without cauterization of the residual cyst. These lesions frequently recur. Marsupialization of deep orbital dermoids may then be justified as an attractive alternative to extensive orbital surgery or neurosurgery with possible complications. The functional eye with good vision and fusion is well worth the cosmetic deficit of proptosis and the annoyance of intermittent discharge from the fistula. (17 figures, 25 references)—Author's abstract

DRUSEN OF THE OPTIC DISK-HEMORRHAGIC COMPLICATIONS. Sanders, T. E., Gay, A. J. and Newman, M. (Washington University School of Medicine, St. Louis, Mo.), Tr. Am. Ophth. Soc. 68:186-218, 1970.

Drusen of the optic nerve head are associated with three types of hemorrhage complications. One is the splinter hemorrhages in the substance of the disk. These apparently are asymptomatic, but theoretically they may play a role in the field loss associated with drusen. The main problem they present is in the differentiation of drusen from papilledema. The location of the hemorrhages in the disk and the characteristic fluorescein angiography should serve to clarify the diagnosis. The second type is the disk hemorrhage that is severe enough to rupture into the vitreous body. This results in blurred vision but usually resolves without complication. It is important to realize that drusen of the optic nerve can be a cause of vitreous hemorrhage. Third is the deep peripapillary hemorrhage lying beneath the retina, with associated blurred vision. It apparently resolves, leaving a peripapillary pigment atrophy similar to that occurring after inflammatory juxtapapillary processes. This type may also form a localized hematoma simulating melanoma. A central field defect is usually present in both forms. (13 figures, 21 references)—Authors' abstract

RESTRICTION IN UPWARD GAZE WITH ADVANCING AGE. Chamberlain, W., Tr. Am. Ophth. Soc. 68:234-244, 1970.

A progressive symmetrical limitation in upward gaze with advancing years has been

documented. This limitation of elevation is most apparent in the elderly, but is a measurable restriction, which can be demonstrated even in young adults. The symmetrical restriction of upward gaze simulates a supranuclear paralysis. When there is a marked inability to elevate either eye, it is not possible to test the function of the individual muscles that elevate the globe. In evaluating older patients it is important to recognize that symmetrical limitation of upward gaze may be a "normal" finding related to the age of the individual. The normal upward rotation in young children in the 5 through 14-year decade is 40°, but in elderly patients in the 75 to 84-year bracket the average is only 16° with many scarcely able to elevate 10°. It would seem that the relative ineffectiveness of upward gaze may relate to the reduced use of the eyes in the upper field with advancing years. (5 figures, 2 tables, 9 references)—Author's abstract

HYDRATION OF THE CORNEA. Manchester, Jr., P. T., Tr. Am. Ophth. Soc. 68:425-461, 1970.

There are variations in corneal hydration as evidenced by changes in its thickness, curvature, and transparency. The cornea becomes thicker and flatter during sleep, although it does not seem to vary during pregnancy, with birth control drugs, or during the phases of the menstrual cycle. Removal of the precorneal oily film by irrigation, then exposure of the eye during surgery may cause considerable thinning of the cornea. Contact lenses cause very slight reversible thickening of the cornea. They also mould and warp the surface of the cornea and they produce superficial cloudiness which can be seen grossly by scleral shatter technique. They may cause alteration of the protective pre-corneal oily film with resultant development of dry spots and ulceration. (18 figures, 13 tables, 54 references)—Author's abstract

## TRANSACTIONS OF THE PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

FILTERING CONJUNCTIVAL BLEBS AS A COMPLICATION OF CATARACT EXTRACTION. Christensen, R. E. and Rundle, H. L. (Jules Stein Eye Institute, Los Angeles), Tr. Pac. Coast Oto.-Ophth. Soc. 51:137-156, 1970.

In a consecutive series of 710 cataract extractions, unintentional postoperative filtering blebs occurred in 18 eyes. Seventeen of the 18 blebs (90%) appeared within seven months after surgery. Filtering blebs after limbus based conjunctival flaps occurred seven times more frequently than after fornix based conjunctival flaps. Postoperative complications were the most common etiologic factor associated with the production of the filtering blebs. Site of suture placement, incision site into the anterior chamber, use of enzymatic zonulysis, or operative complications could not be correlated either with the development, size, or location of the blebs. Seven of the 18 eyes had hypotony, yet the size of the blebs could not be correlated with the degree of hypotony. In this series, hypotony did not appear to affect visual acuity adversely. Indications for operative bleb closure include foreign body sensation, tearing, persistent leakage of aqueous, interference with contact lens wear, and macular edema. (7 figures, 4 tables, 14 references)—Authors' abstract

SURGICAL TREATMENT OF JAW-WINKING PTOSIS. Berke, R. N. (Palo Alto, California), Tr. Pac. Coast Oto.-Ophth. Soc. 51: 215-216, 1970.

The author performed 55 operations of various kinds for surgical correction of jaw-winking ptosis. He concludes that the best results follow a Crowell Beard operation in which both levator muscles were myectomized and both lids suspended from the brows by autogenous fascia lata. (7 references)—David Shoch

PHOTOCOAGULATION OF EXUDATIVE SENILE MACULOPATHY. Cleasby, G. W., Fung, W. E. and Fiore, Jr., J. V. (San Francisco, Calif.), Tr. Pac. Coast Oto.-Ophth. Soc. 51:233-258, 1970.

Sixty-two cases are described in which photocoagulation treatment of ESM was employed. The results have been generally encouraging. The authors believe that carefully directed photocoagulation by presently available techniques, in selected cases, can be useful in preserving vision for these unfortunate patients. (18 figures, 11 references)—David Shoch

# NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
*700 North Michigan Avenue, Chicago, Illinois 60611*

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### FIRST PAN AMERICAN SYMPOSIUM ON STRABISMUS

The First Pan American Symposium on Strabismus, sponsored by the Pan American Association on Ophthalmology, will be held at the Shands Teaching Hospital, University of Florida, Gainesfille, Florida, on March 30-31, 1972. This meeting immediately precedes the Ninth Pan American Association of Ophthalmology Meeting in Houston, Texas.

It will consist of presentations by a distinguished panel, followed by round table discussions.

The moderators will be Alberto Ciancia (Argentina), John Pratt-Johnson (Canada), Guilllermo Velez Restrepo (Colombia), and Gunter K. von Noorden, Edward Dunlap, and Marshall M. Parks (U.S.A.).

For further information regarding this meeting, please write to Jorge Ferrer, M.D., Department of Ophthalmology, Medical College, University of Florida, Gainesville, Florida 32601.

### DOMINICAN REPUBLIC RECEIVES GRANT FROM INTERNATIONAL EYE FOUNDATION

As part of a continuing program of assistance to the Dominican Republic, the International Eye Foundation has sent $10,000 worth of examining and surgical equipment to the Doctor Luis E. Aybar Hospital in Santo Domingo. All of this equipment was donated to thte IEF by pharmaceutical houses and individual ophthalmologists.

In addition to the Dominican Republic, the IEF is presently conducting assistance programs in Puerto Rico, El Salvador, Honduras, and Haiti. The Foundation is planning additional projects throughout Latin America. As part of its Latin American Fellowship program, the IEF arranges annually for 20 resident eye surgeons to attend the University of Puerto Rico's basic science course in ophthalmology.

### EIGHT STUDENT FELLOWSHIPS AWARDED: FIGHT FOR SIGHT

Eight Student Fellowships have been awarded for 1971 by Fight For Sight, Inc., it was announced by Charles A. Perera, Chairman of the organization's Scientific Advisory Committee. Recipients are Walter E. Bundy, Department of Ophthalmology, Virginia Commonwealth University, Richmond, Virginia (Direct supervisor: Walter J. Geeraets; project title: The effect of vitamin A on the healing of experimental corneal lesions; Amount: $600). Wei-Mei Ching, Department of Chemistry, Natural Science II, University of California, Santa Cruz, California (Direct supervisor: Edward A. Dratz; project title: Structure and function of the visual membrane; amount: $750). Joseph Eichenbaum, Bascom Palmer Eye Institute, University of Miami, Miami, Florida (Direct supervisor: Duco I. Hamasaki; project title: Response of normal and visually deprived neurons of cats to moving stimuli; amount: $600). Stephen Finger, Department of Ophthalmology, Columbia University, New York, New York (Direct supervisor: Emil Wirostko; project title: Is there an infectious agent in the etiology of diabetic retinopathy? amount: $600). Laurence Franklin, Department of Chemistry, Natural Science II, University of California, Santa Cruz, California (Direct supervisor: Edward A. Dratz; project title: The mechanism of visual excitation; amount: $750). Robert P. Goodman, Department of Biochemistry, Virginia Commonwealth University, Medical College of Virginia, Richmond, Virginia (Direct supervisor: James M. Collins; project title: Alteration of DNA during lens cell differentiation; amount: $875. Susan Bagley Johnson, The Marine Biological Laboratory, Woods Hole, Massachusetts (Direct supervisor: Seymour Zigman; project title: Near ultraviolet effects on visual cell biochemistry: Amount: $750). Charles L. Murphy, Department of Biochemistry, University of Georgia, Augusta, Georgia (Direct supervisor: John Lee; project title: Photoenzymes; amount: $750).

### OPHTHALMOLOGY SELF-EDUCATION PROGRAM

Fellows of the American Academy of Ophthalmology and Otolaryngology are offered an ophthalmology self-education program without charge. It provides an outline containing the essential core of ophthalmic knowledge and provides select areas for study in accordance with the personal needs or preferences of the ophthalmologists. It provides two major study guides, reading lists, and self-assessment procedures each year. It is conducted under the auspices of Bradley R. Straatsma and the Academy Group in Continuing Education in Ophthalmology.

The new program is designed primarily to assist the practicing ophthalmologist in maintaining a continuing process of education throughout his professional life.

Applications and further information may be obtained from C. M. Kos, M.D., Executive Secretary-Treasurer, American Academy of Ophthalmology and Otolaryngology, Continuing Education in Ophthalmology, 15 Second Street SW, Rochester, Minnesota 55901.

### Short course tuition fees: Armed Forces Institute of Pathology

The Board of Governors at the Armed Forces Institute of Pathology Washington, D.C., decided a tuition fee of $25 per day will be charged to each civilian attending postgraduate short courses in continuing education. The action is effective as soon as possible, following modification of the wage-price policy.

A five-day course in ophthalmic pathology is scheduled for February 28 to March 3, 1972. Further information is available from the Armed Forces Institute of Pathology, Washington, D.C. 20305.

### Spring Meeting: West Virginia Academy of Ophthalmology and Otolaryngology

The National Spring Meeting of the West Virginia Academy of Ophthalmology and Otolaryngology will be held April 26-29, 1972, at the Greenbrier Hotel, White Sulphur Springs, West Virginia.

The ophthalmology program will be highlighted by Miles A. Galin, New York; Louis J. Girard, Houston; Frank W. Newell, Chicago; John T. Simonton, New York; and Frederick Stocker, Durham.

Hotel reservations should be made directly with the Greenbrier Hotel. The registration fee of $60 should be made payable to the West Virginia Academy of Ophthalmology and Otolaryngology and sent to J. Elliott Blaydes, Jr., M.D., 107 Federal Street, Bluefield, West Virginia.

### Symposium: University of Louisiana School of Medicine

The Department of Ophthalmology of the Louisiana State University School of Medicine announces a symposium on glaucoma, to be held at the L.S.U. Medical Center in New Orleans, Louisiana, on January 21-22, 1972. Guest participants at the symposium will be W. Morton Grant of Harvard University, Robert N. Shaffer of the University of California, H. Dunbar Hoskins, Jr., of the University of California, David Walton of Harvard University, David Apple of the University of Illinois, and William H. Coles of the University of South Carolina. Registration fee, payable to the Eye Foundation of America, is $100. For further information, contact George M. Haik, M.D., Department of Ophthalmology, L,S.U. Medical Center, 1542 Tulane Avenue, New Orleans, Louisiana 70112.

### Journal of Ophthalmic Surgery

The Journal of Ophthalmic Surgery is being reorganized under the editorship of George W. Weinstein, Head of the Division of Ophthalmology of the University of Texas Medical School at San Antonio. Members of the editorial board include Walter R. Gilbert, Jr., Jacksonville, Florida; Morton F. Goldberg, Chicago; Eugene Helveston, Indianapolis; Steven Ryan, Baltimore; Charles R. Leone, Jr., San Antonio; Margaret F. Obear, New York; Richard Keates, Columbus, Ohio; David Paton, Houston; Richard C. Troutman, New York; and George L. Spaeth, Philadelphia. The Journal appears bi-monthly and includes articles on basic and clinical aspects of surgery, instrumentation techniques, and related aspects of this field.

### Annual ophthalmology department meeting: Hermann Hospital

The third annual meeting of the department of ophthalmology of Hermann Hospital of Houston, Texas, will be held December 11, 1971. The guest speaker is Charles L. Schepens of Boston, Massachusetts.

### Postgraduate seminar: Cleveland Clinic

The annual postgraduate seminar of the ophthalmology department of the Cleveland Clinic Foundation will be held December 8-9, 1971. The guest faculty includes Morton F. Goldberg, Thomas R. Hedges, Eugene M. Helveston, and John R. Lynn. F. A. Gutman is chairman of the seminar.

For further information write to the Education Office, Cleveland Clinic Foundation, Cleveland, Ohio 44106.

### Contact lens course: Baylor College of Medicine

The contact lens course of the department of ophthalmology of Baylor College of Medicine, Houston, Texas, will be held December 9-11, 1971. The course is open to all ophthalmologists, residents in ophthalmology, and technicians sponsored by an ophthalmologist. Classes will be conducted so that each ophthalmologists will be given individual instruction by members of the staff of the department of ophthalmology and guest lecturers.

For further information contact David Paton, M.D., Professor and Chairman, Department of Ophthalmology, Baylor College of Medicine, 1200 Moursund, Houston, Texas 77025.

### Technicians course: International Eye Foundation

The International Eye Foundation established a three-month course for ophthalmic technicians in Indonesia, beginning in October, 1971. Katherine Burkhard, a graduate of Georgetown University's school for ophthalmic technicians, will teach the course. Technicians who complete the course will be qualified to assume much of the responsibility of the treatment and diagnosis of minor eye diseases. This will permit the 12 ophthalmologists in Djakarta to concentrate on more technical aspects of ophthalmology and treating patients in need of immediate care.

In addition, Suzanne Veronneau and Richard C. Troutman of New York will serve as a medical teaching team in Indonesia from late October through November.

### Presidents' Meeting: Puget Sound Academy

The annual presidents' meeting of Puget Sound Academy of Ophthalmology will be held January 14 and 15, 1972, at the Wahington Plaza Hotel,

Seattle. The theme of the program will be complications of ophthalmic surgery. Speakers include Benjamin F. Boyd, Milton Boniuk, and Jerome W. Bettman. Management of office problems will be discussed in a seminar.

Further information is available from William P. Mulligan, M.D., 4615 35th Avenue S.W., Seattle, Washington 98126.

### Coming meetings

Research Study Club Mid-Winter Clinical Convention at Los Angeles Hilton Hotel, January 23-28, 1972. Information: 1136 West 6th Street, Los Angeles, California 90017.

Third Mid-Winter Ophthalmological Conference at St. Mary's Hospital nad Medical Center, January 22, 1972. Information: 2200 Hayes Street, San Francisco, California.

The 58th Annual Colorado Ophthalmology Conference at Broadmoor Hotel, July 3-6, 1972. Information: University of Colorado Medical School, Office of Postgraduate Medical Education, 4200 East Ninth Avenue, Denver, Colorado 80220.

Ophthalmic Plastic and Corneal Symposium at Diplomat Hotel, Hollywood, March 26-31, 1972. Information: Bascom Palmer Eye Institute, Box 875, Biscayne Annex, Miami, Florida 33152.

Ninth Annual Neuro-Ophthalmology Course at Americana Hotel, Miami Beach, January 4-7, 1972. Information: Bascom Palmer Eye Institute, Box 875, Biscayne Annex, Miami, Florida 33152.

Florida Midwinter Seminar at American Hotel, Miami Beach, January 30 to February 5, 1972. Information: Bascom Palmer Eye Institute, Box 875, Biscayne Annex, Miami, Florida 33152.

Clinical Conference of Chicago Ophthalmological Society at Drake Hotel, Chicago. Information: 950 East 59th Street, Chicago, Illinois 60637.

Ophthalmology meeting of the University of Kansas School of Medicine, Department of Postgraduate Medical Education, from April 10-12, 1972. Information: 39th and Rainbow Blvd., Kansas City, Missouri 66103

Wilmer Residents Meeting at Turner Auditorium, April 13-15, 1972. Information: Johns Hopkins University School of Medicine, 725 N. Wolfe, Baltimore, Maryland 21205.

Neuro-Ophthalmology meeting at Massachusetts Eye and Ear Infirmary April 24-29, 1972. Information: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115.

Ophthalmology for the Internist, Pediatrician, and General Practitioner at Massachusetts Eye and Ear Infirmary, May 4-5, 1972. Information: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115.

Diseases of the Cornea at Massachusetts Eye and Ear Infirmary, June 8-10, 1972. Information: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, Massachusetts 02115.

Ophthalmology Conference, University of Michigan May 11-13, 1972. Information: Towsley Center for Continuing Medical Education, University of Michigan Medical Center, Ann Arbor, Michigan 48104.

Ophthalmology for Specialists at Nolte Center for Continuing Education, May 1-2, 1972. Information: Health Sciences Center, University of Minnesota Medical School, Box 193, Minneapolis, Minnesota 55455.

Ophthalmic plastic surgery, Brooklyn Eye and Ear Hospital, April 26-28, 1972. Information: 29 Greene Avenue, Brooklyn, New York 11238.

Annual Spring Meeting and Postgraduate Course in Ophthalmology and Otolaryngology, University of Oklahoma Medical Center, March 16-17, 1972. Information: University of Oklahoma Medical center, 800 Northeast 13th Street, Oklahoma City, Oklahoma 73104.

Postgraduate Convention, Oregon Academy of Ophthalmology and Otolaryngology, March 3-4, 1972. Information: Oregon Academy of Ophthalmology and Otolaryngology, 1216 SW Yamhill Street, Portland, Oregon 97205.

Fourth Annual Seminar of the Department of Ophthalmology, New York Medical College, Dorado Beach Hotel, Puerto Rico, January 14-22, 1972. Information: Department of Ophthalmology, New York Medical College, 1249 Fifth Avenue, New York, New York 10029.

Annual Residents Conference, Medical University of South Carolina, April 6-8, 1972. Information: Department of Ophthalmology, Medical University of South Carolina, 80 Barre Street, Charleston, South Carolina 29401.

### Personals

#### Trustees' award: Research to Prevent Blindness

The Research to Prevent Blindness Trustees' award for outstanding achievement was awarded to David H. Hubel and Torsten N. Wiesel September 22, 1971, during the annual meeting of the American Academy of Ophthalmology and Otolaryngology. Both are professors of neurobiology at Harvard University Medical School. The award was made by Jules C. Stein, Chairman of Research to Prevent Blindness, Inc. It consists of a plaque and a $25,000 honorarium from personal contributions of the board of trustees of Research for the Prevention of Blindness. Previous recipients of the award are Frank B. Walsh (1966); Charles L. Schepens and Gard Meyer-Schwickerath (1967); and Toichiro Kuwabara (1969).

Doctors Hubel and Wiesel (Fig. 1) studied extensively the electrical activity of individual neurons of visual centers in the brain of kittens and monkeys. They have studied the effects of visual deprivation and the morphologic and physiologic properties of visual cells, as well as the processing of information concerning the directions center intensity of stimuli of the eyes.

#### Samuel Schwartz

Samuel Schwartz has been appointed Deputy Associate Director for Extramural Programs, Na-

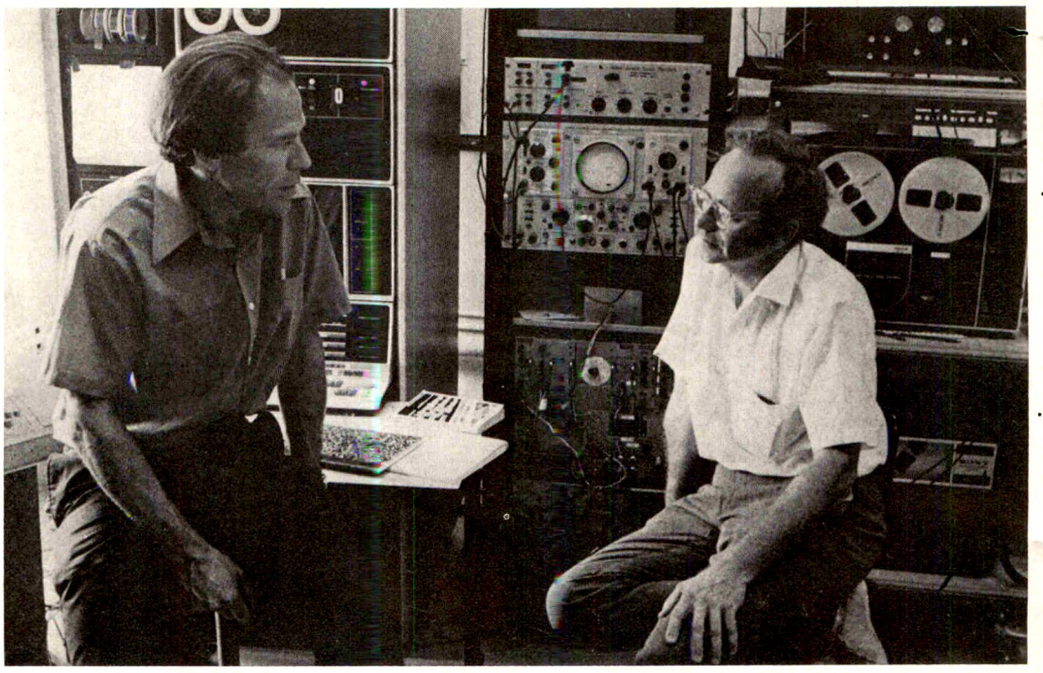


Fig. 1 (Hubel and Wiesel). Drs. Torsten N. Wiesel (left) and David H. Hubel (right), recognized for outstanding achievement in ophthalmology by Trustees of Research to Prevent Blindness.

tional Eye Institute, by Dr. Carl Kupfer, NEI Director.

Dr. Schwartz will also serve as Chief, Scientific Programs Branch of the NEI Extramural Programs, succeeding Dr. Samuel Price. In both capacities, Dr. Schwartz will assist Dr. George Brooks, newly appointed Associate Director for Extramural Programs, in directing the over-all scientific and administrative management of NEI's research and training programs.

A native of Winnipeg, Canada, Dr. Schwartz earned a B.Sc degree from the University of Manitoba in 1952 and a Ph.D. degree from the University of Minnesota in 1956, majoring in medicinal chemistry with a minor in biochemistry. He served for eight years on the faculty of the George Washington University.

Dr. Schwartz brings to NEI a varied background in NIH extramural activities beginning in 1964 with the National Cancer Institute. In January, 1965, he was appointed Executive Secretary of the Medicinal Chemistry Study Section, Division of Research Grants (DRG) and served in that capacity until November, 1968. As Assistant Chief for Referral, Research Grants Review Branch, DRG, he then assumed responsibility for the DRG Research Referral Office and held that position until his present appointment.

### Arthur H. Wolintz

Arthur H. Wolintz, Clinical Assistant Professor of Ophthalmology at State University of New York, Downstate Medical Center, Brooklyn, has been named Associate Director of Neurology, Coordinator in Ophthalmology and Neuro-Ophthalmologist at the Kingsbrook Jewish Medical Center. Dr. Wolintz, who resides in Brooklyn, attended New York University. He was graduated Summa Cum Laude from the State University of New York, Downstate Medical Center College of Medicine in 1962. He served his internship and one year of medical residency at Maimonides Medical Center. He was a resident in neurology in the Medical Neurology Branch of the National Institute of Neurological Disease and Blindness and served as senior and chief resident in neurology at Mount Sinai Hospital. He was awarded a special fellowship in neuropathology at the College of Physicians and Surgeons, Columbia University. He completed training in ophthalmology and neuro-ophthalmology at Downstate Medical Center in 1971.

### More volunteers for Project HOPE

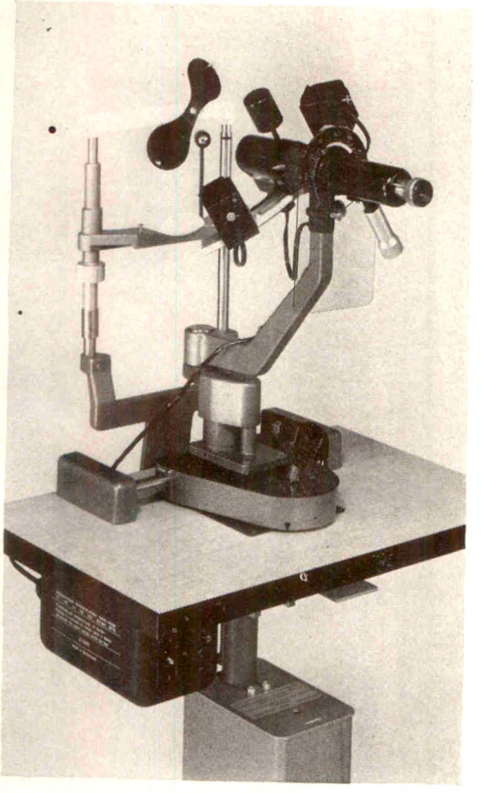
Ophthalmologists Robert James Davis, Patrick D. Moore, and Brooks Poley are now serving short-term tours of service on the hospital ship SS HOPE, beginning October 1. The good ship HOPE is now in Kingston in the West Indies on a 10-month medical teaching and treatment mission.

Dr. Davis is in private practice in Spokane, Washington. Dr. Moore is a resident at Wills Eye Hospital in Philadelphia. Dr. Poley is an instructor in ophthalmology at the University of Minnesota School of Medicine in Minneapolis.

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For information contact: Retinal Service
Department of Ophthalmology
University of Iowa College of Medicine
Iowa City, Iowa 52240



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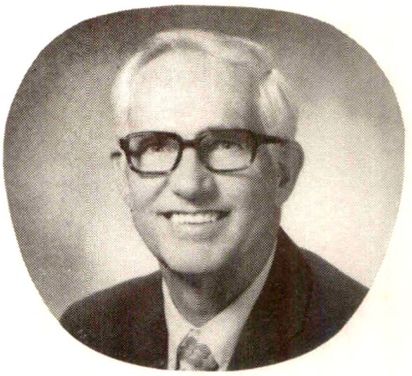
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Tuition is $600.00. For further information and application forms please write to Whitney G. Sampson, M.D., Coordinator of Basic Science Programs, Department of Ophthalmology, The University of Texas Medical School, 530 West 20th Street, Houston, Texas 77008.

# Tillyer Topics



E. WILLIAM TILLYER

## Aspheric Cataract Lenses

Of all the work done in optics for the betterment of vision, perhaps the most spectacular is the development of aspheric cataract lenses. Nowhere can I recall such dramatic improvement in the quality of vision as that which occurs when properly developed aspheric curves are used in place of spherical curves in the aphakic patient's prescription.

The patient's reaction, of course, is the ultimate criterion. But the advantages of the aspheric curves can be proved mathematically.

For instance, a +14.00 sphere, if made up in a spherical curve with a —3.00 D inside curve, has the following Rx at 15mm away from the center of lens:

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$$+14.31 = -.75$$

This is quite a dramatic reduction in the marginal error. It is no wonder so many patients are extremely pleased with their new aspheric lenses!

But just being an aspheric lens does not make all the difference. One cannot use the same aspheric curve for all Rx's and still get these same results. The marginal effects of each power of sphere combined with each cylinder must be computed. Then a determination can be reached of the best aspheric curves for the individual power required.

We use 29 different base curves in the range from plus 8.00 D to plus 20.00 D. Only with this minimum can we achieve what we consider the ultimate results.

This seems like a lot of changes—more than one for every half diopter change in Rx power. But it gives the patient better vision every time.

There are other areas where improvements have been made in lens design which are extremely important. But I, personally, still believe that none are as dramatic as the vision given the aphakic patient—by the use of a true aspheric series of cataract lenses.

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# The American Society of Contemporary Ophthalmology



## annual meeting

**February 27-March 3, 1972**
**Diplomat Hotel-Hollywood, Florida**

**MONDAY 9:00 A.M.**
**February 28**

**Cancer Symposium**
George Moore, M.D.
Chairman
Harvey Lincoff, M.D.
Bernard Fisher, M.D.
Frederic Mohs, M.D.
Setrag Zacarian, M.D.
Andrew Gage, M.D.
Ruth Long, M.D.

**2:00 P.M. to 5:00 P.M.**

Jules Francois, M.D.
Chairman
Yi-Yung Hsia, M.D.
Theo. Schlaegel, M.D.
Edward Dunlap, M.D.
Sidney Fox, M.D.
Crowell Beard, M.D.
Lawrence Harris, M.D.
Byron Smith, M.D.
Pierre Guibor, M.D.

**ENTERTAINMENT FOR WIVES AND CHILDREN**

**Golf, Tennis and Swimming**

**TUESDAY 9:00 A.M.**
**February 29**

**Cataract Symposium**
Harold Scheie, M.D.
Chairman
Robert Schimek, M.D.
Norman Jaffe, M.D.
Miles Galin, M.D.
Ralph Kirsch, M.D.
John Bellows, M.D.

**2:00 P.M. to 5:00 P.M.**

**Glaucoma and Lid. Surgery**
Saul Sugar, M.D.
Chairman
Miles Galin, M.D.
Lawrence Harris, M.D.
Dohlman, Claes, M.D.

**WEDNESDAY 9:00 A.M.**
**March 1**

**Rentina Symposium**
Charles Schepens, M.D.
Chairman
Graham Dobbie, M.D.
Michael Shea, M.D.
Harvey Lincoff, M.D.
Kenneth Hovland, M.D.
C. Hilsdorf, M.D.
Long, Ruth, M.D.
Freeman, H., M.D.

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**PRACTICAL COURSES**

**WEDNESDAY and THURSDAY**

**2:00 P.M. to 5:00 P.M.**

Jose Barraquer, M.D.
Chairman

**Microscopic Surgery of the Cornea**

Charles Schepens, M.D.
Chairman

**Binocular Ophthalmoscopy**

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**THURSDAY 9:00 A.M.**
**March 2**

**Corneal Symposium**
Herbert Kaufman, M.D.
Chairman
David Donaldson, M.D.
Stuart Brown, M.D.
Donald Willard, M.D.
Drs. Jose & Francisco Barraquer

**FRIDAY 9:00 A.M.**
**March 3**

**Ocular Infections**
James H. Allen, M.D.
Chairman
Henry F. Allen, M.D.
Herbert Kaufman, M.D.
Roderick MacDonald
Melvin Rubin, M.D.

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April 9-14, 1972

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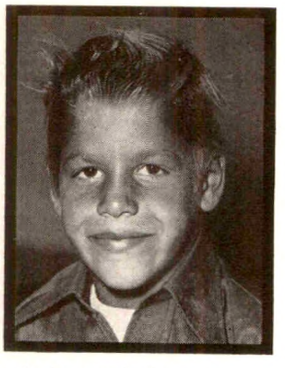
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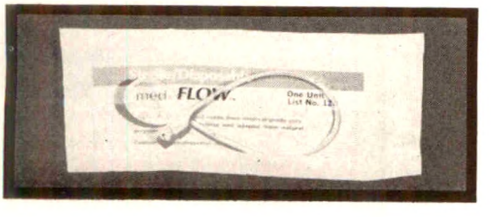
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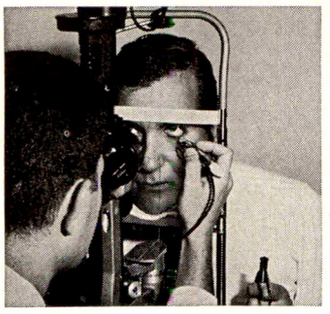
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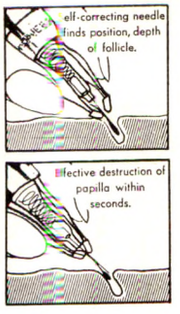
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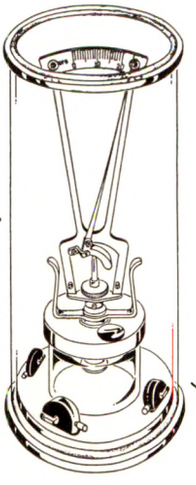
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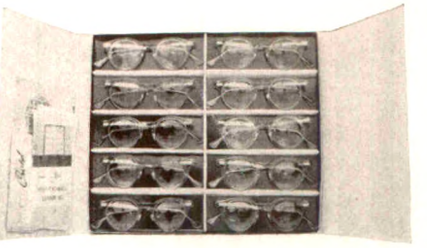
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1. Mishima, S. and D. M. Maurice, The Effect of Normal Evaporation on the Eye, Exp. Eye Res., 1:46, 1961.
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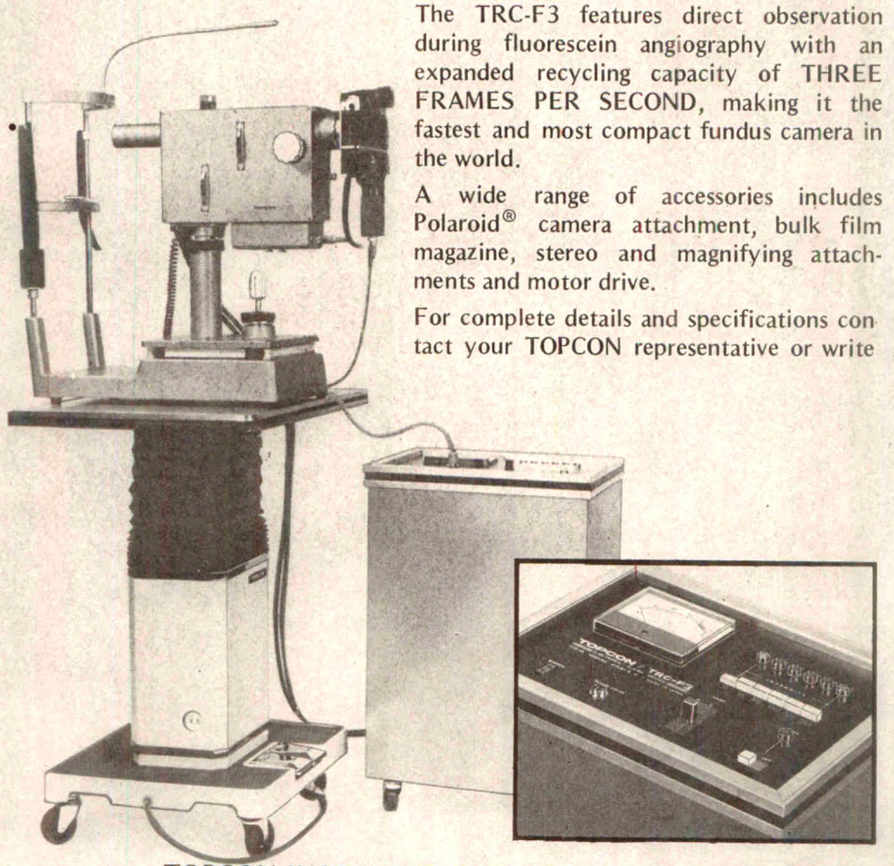
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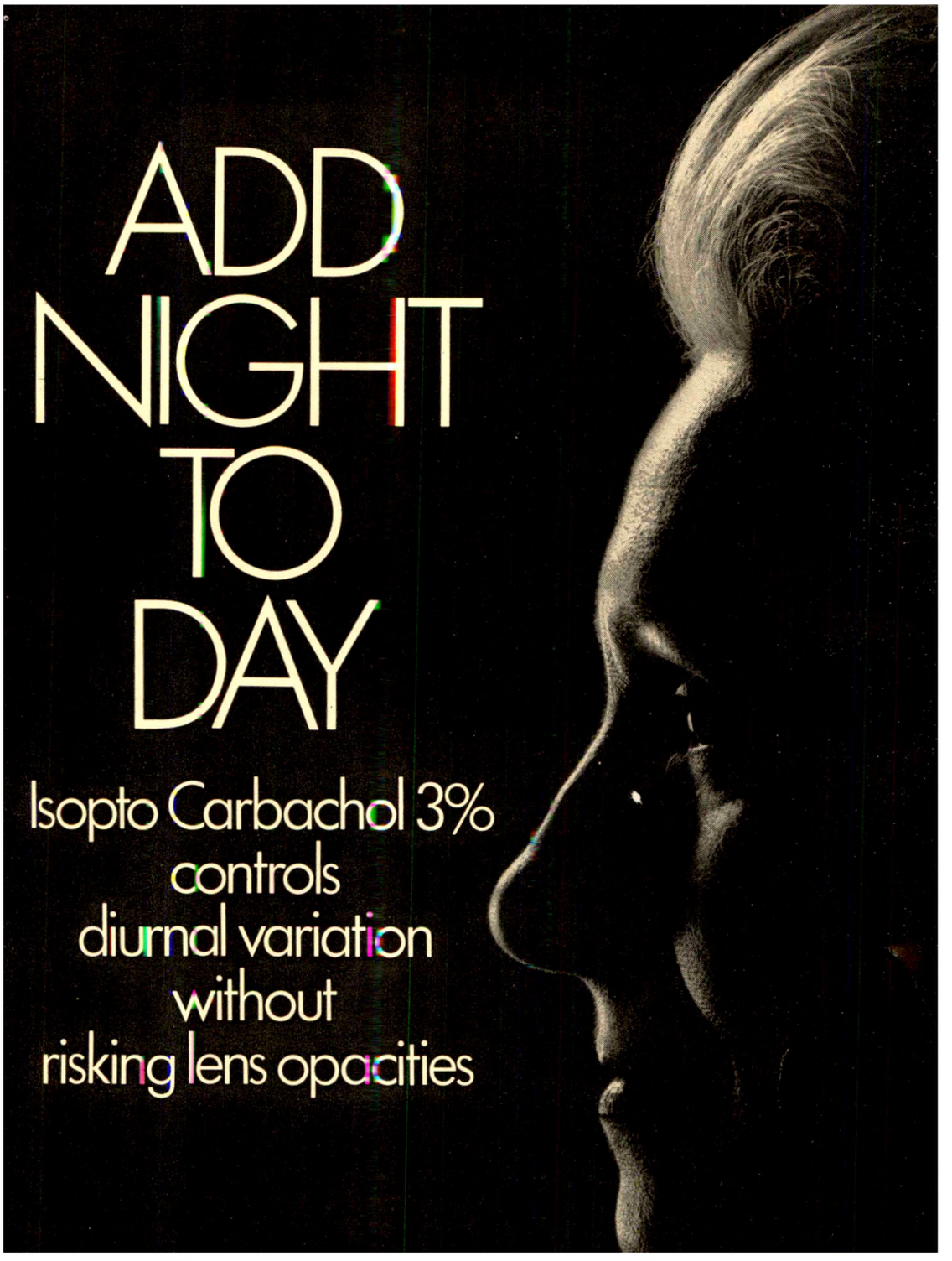
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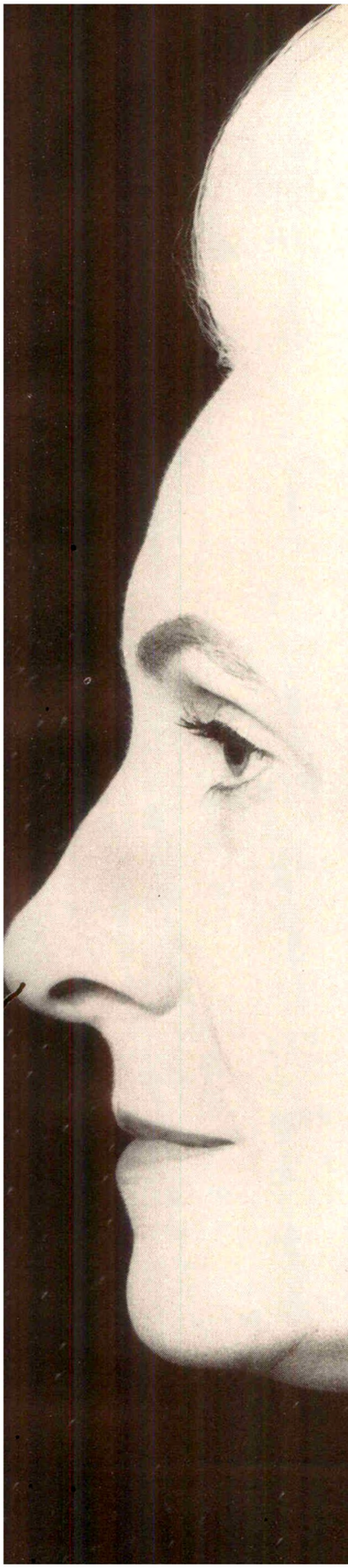
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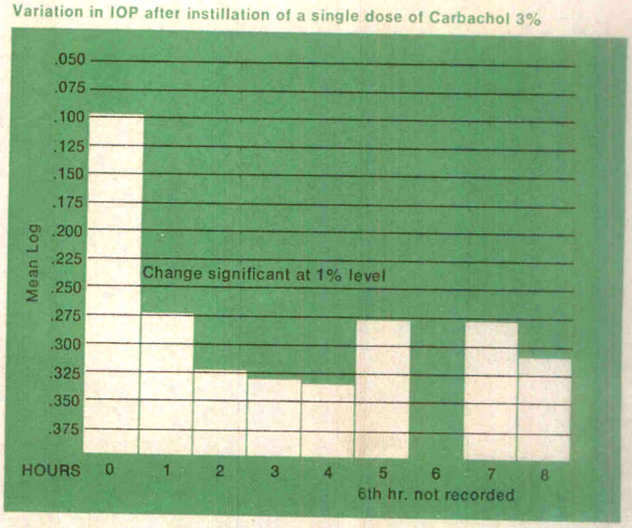

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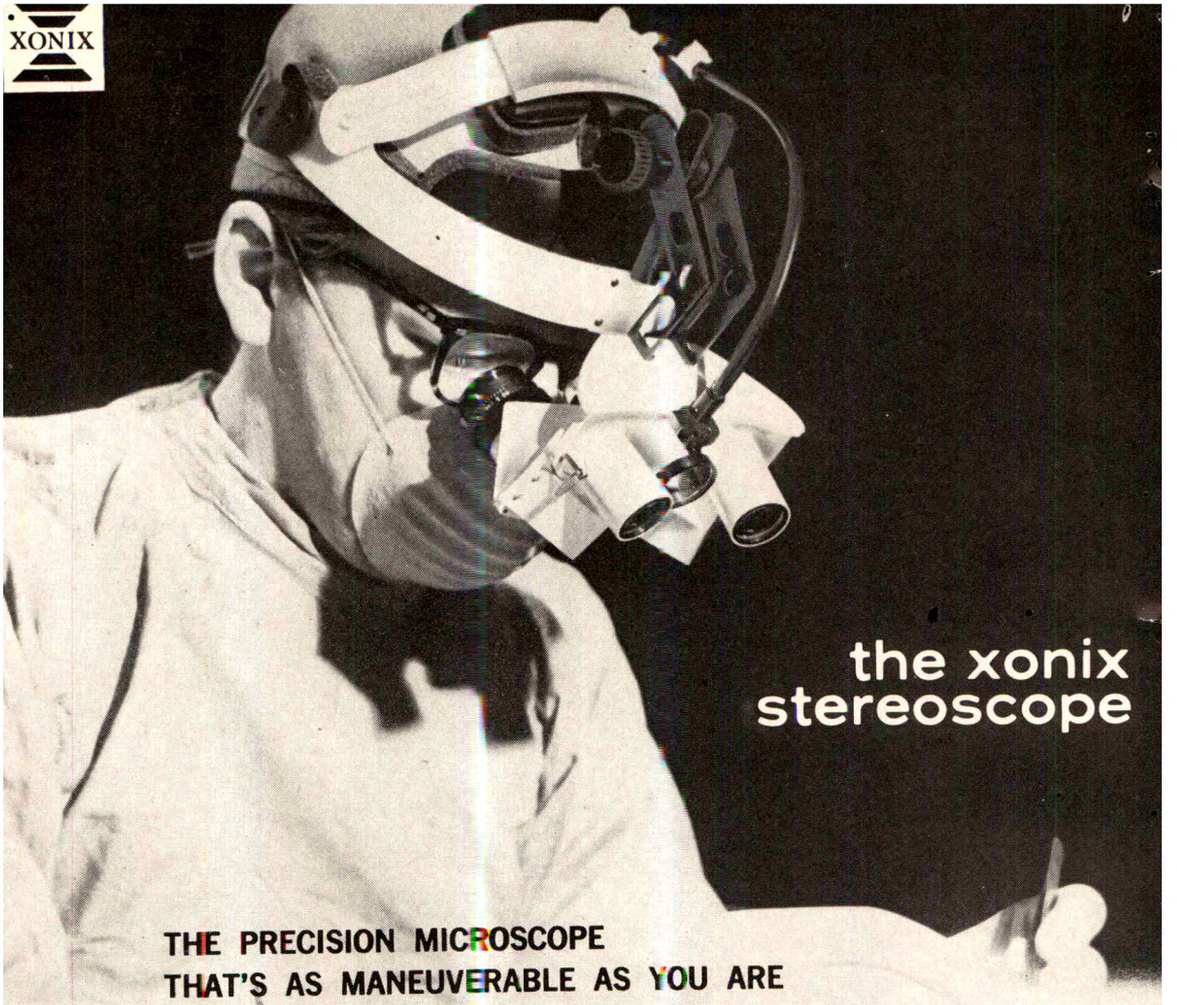
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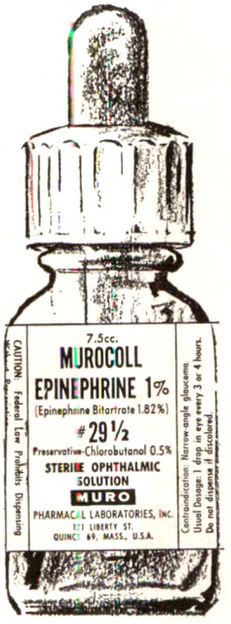
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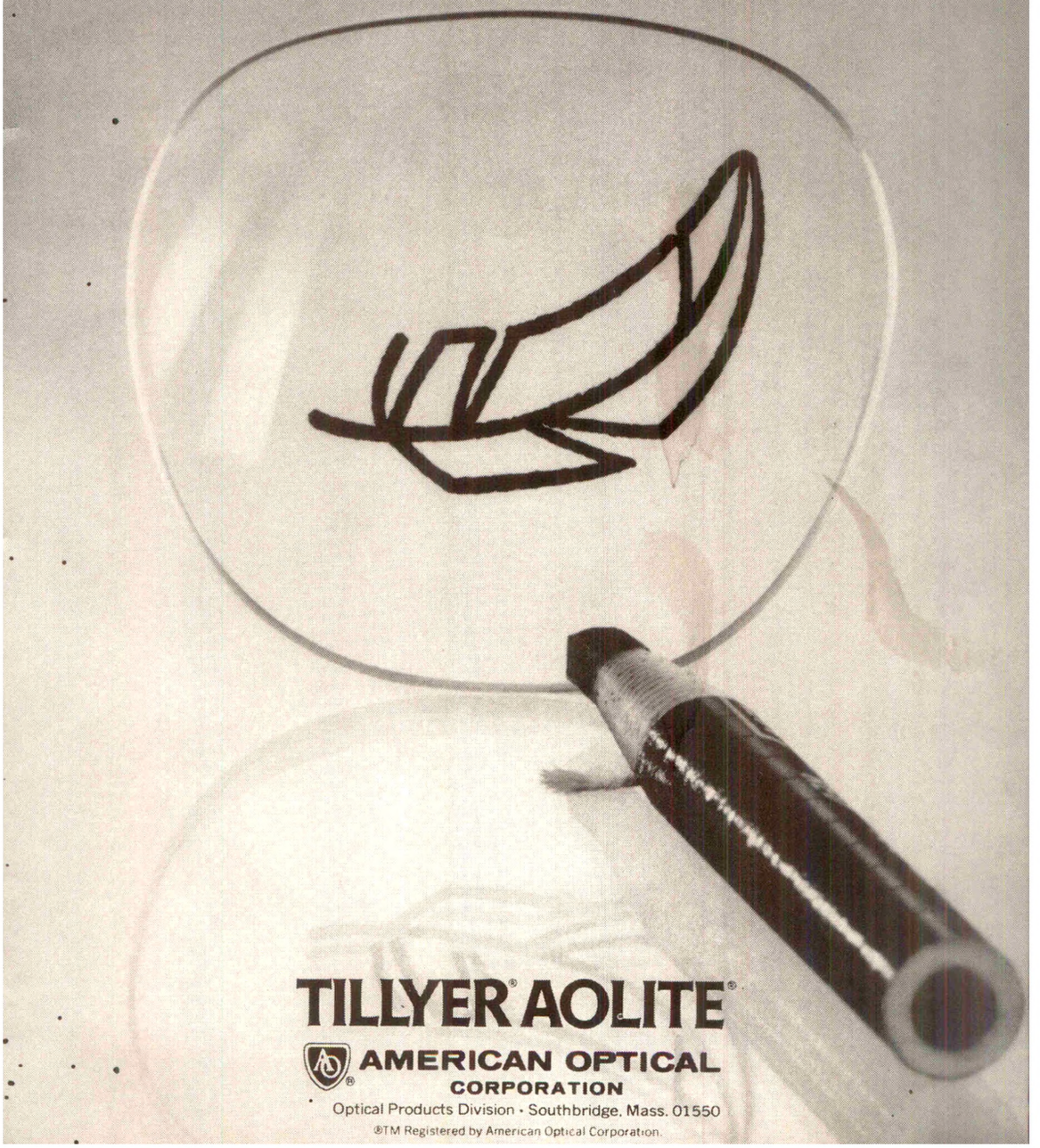
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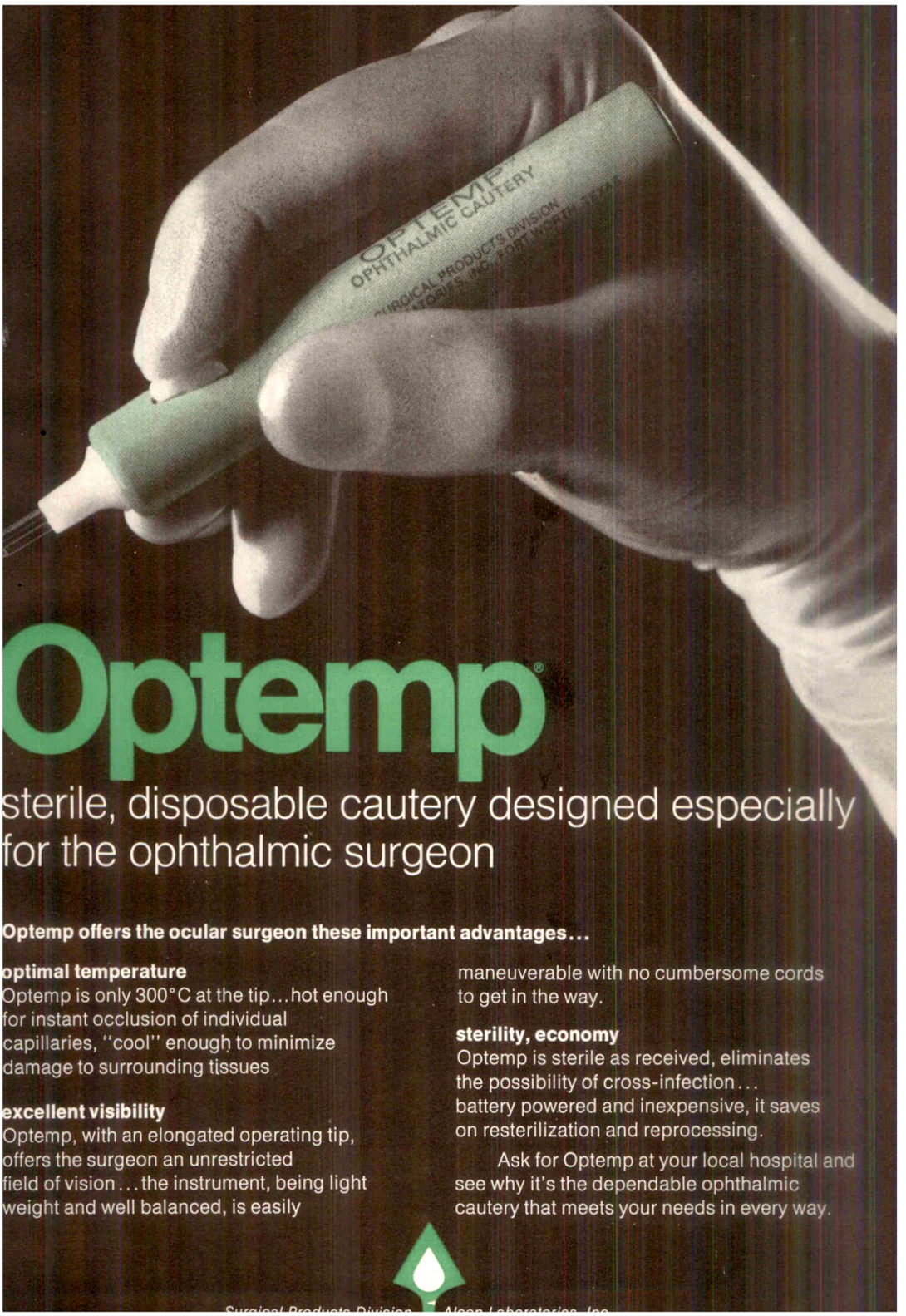
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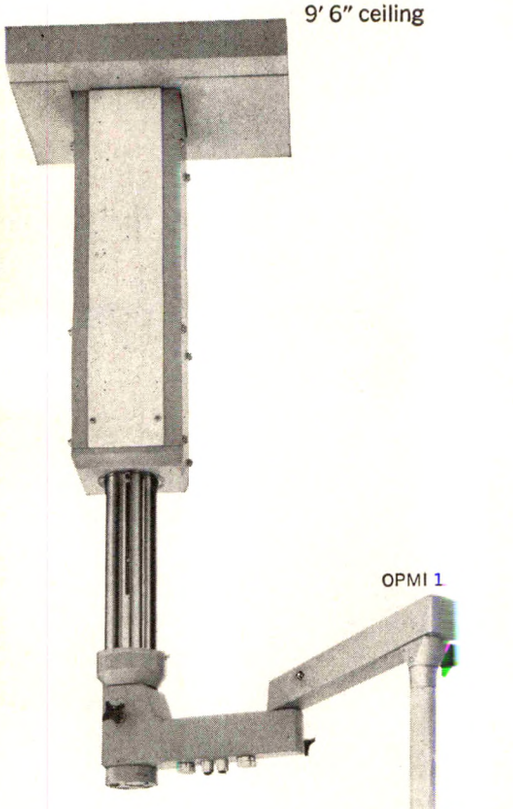
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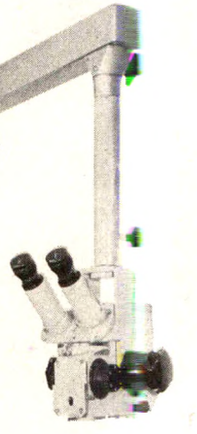



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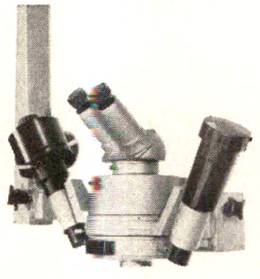
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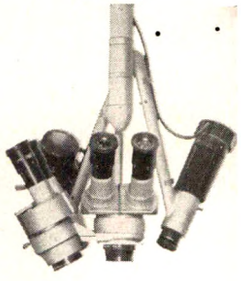
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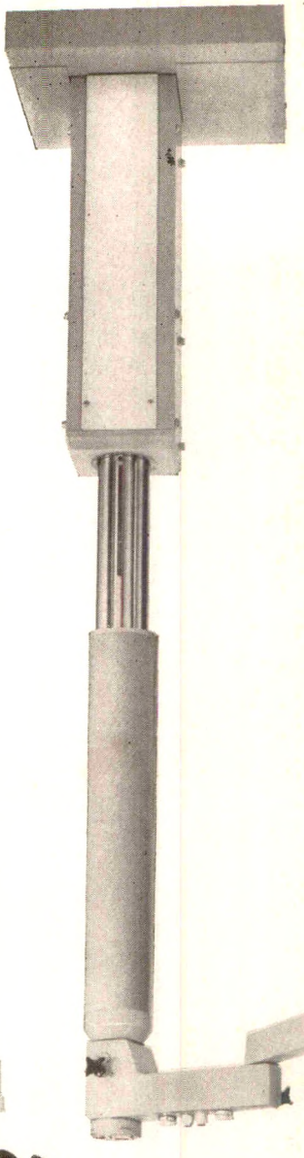
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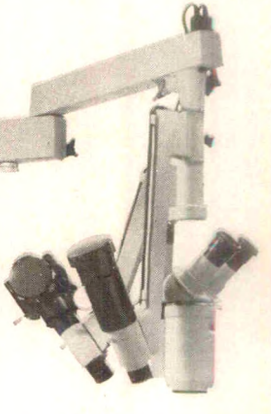
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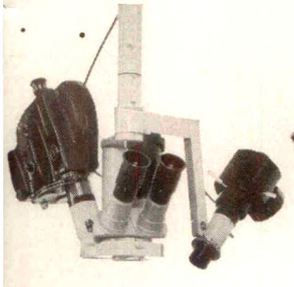
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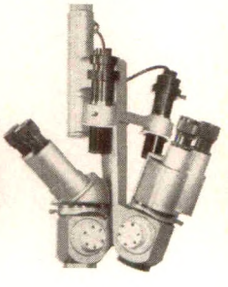
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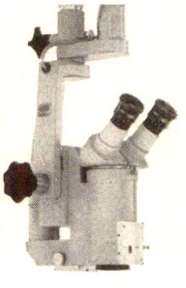
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Thereafter, 1 or 2 drops 2 to 4 times daily.

**COMPOSITION:**

| | |
|---|---|
| Prednisolone-21-phosphate sodium (Equivalent to Prednisolone 0.2%) | 0.25% |
| Sulfacetamide sodium | 10.0% |
| Phenylephrine HCl | 0.125% |
| Methylparaben | 0.02% |
| Propylparaben | 0.005% |

In a stabilized aqueous solution containing sodium thiosulfate and °SMP-68 (a combination of polyoxyethylene polyoxypropylene compound and polysorbate 80).

**EFFECTIVENESS:** The antibacterial spectrum of Vasocidin is particularly effective against the gram positive pyogenic cocci; E. coli, N. gonorrhoeae, Koch-Weeks bacillus and other bacteria susceptible to sulfacetamide. Because Vasocidin is a true solution, dosage is uniform and each drop is free of any irritating particles. The Vasocidin vehicle enhances the dispersion of active components. Sulfacetamide combats a wide range of pathogens; prednisolone reduces inflammatory reaction; phenylephrine relieves hyperemia. Local effects of active therapeutic agents appear to be prolonged by phenylephrine-induced vasoconstriction.

**CAUTION:** Federal law prohibits dispensing without prescription.

**CONTRAINDICATIONS:** Steroids are contraindicated in dendritic ulcers (herpes simplex), vaccinia, varicella and most other viral diseases of the cornea and conjunctiva, as well as in fungal and tubercular ocular disease. Contraindicated in the treatment of purulent conjunctivitis or blepharitis. Should not be used by persons with narrow-angle glaucoma or those sensitive to sulfonamides. If irritation persists or increases, discontinue use and consult physician.

**SIDE EFFECTS:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

Vasocidin is sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of bottle. Keep container tightly closed.

**SUPPLIED:** Plastic dropper-tipped vials, 5 cc.

Smith, Miller & Patch, Inc.,
902 Broadway, New York, N.Y. 10010

**FELLOWSHIPS AVAILABLE**

•

The Heed Ophthalmic Foundation provides fellowships for advanced study or research in ophthalmology. Applicants must be graduates of medical schools accredited by the American Medical Association and citizens of the United States. Deadline for submission of applications: December 31 for a fellowship starting the following July. Please direct all inquiries and requests for application forms to:

DAVID SHOCH, M.D.
Executive Secretary
THE HEED OPHTHALMIC FOUNDATION
303 EAST CHICAGO AVENUE
CHICAGO, ILLINOIS 60611

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Four to six insertions, depending upon availability of space, of one-fourth page black and white advertisement. Copy must be received at least nine months in advance.

**$150 total cost** (no commissions)
**Regular price: $360**

# *Kowa* SL
## slit lamp microscope

*The new portable approach to ophthalmic examination.*




The Kowa SL has removed all limitations placed on the use of the slit lamp microscope by conventional, bulky, fixed instrumentation.

Hand-held and fully portable, the Kowa SL permits ophthalmic examination at any time, any place: before or after surgery, at the patient's bedside, in the nursery . . . anywhere.

Yet for all its compactness, light weight, moderate price, and remarkable versatility, it has sacrificed nothing in the way of performance or reliability.

The Kowa SL's optics are the finest; its mechanics and electronics are state-of-the-art; it offers an image bright enough for use in a fully illuminated room.

In short, the Kowa SL is one of the most sophisticated slit lamp microscope systems there is . . . and the *only one* that's fully portable.

For the details on the *new portable approach* to ophthalmic examinations, the Kowa SL, contact the representative in your area.

***Kowa Company, Ltd.***
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IMPERIAL OPTICAL COMPANY, LTD.
Toronto, Ontario, Canada

# Before you buy a $25,000 argon laser photocoagulator, invest 

in research.

For such a small investment, you'll discover that our new instrument, with its fiber optics transmission system, is uniquely designed for effective retinal photocoagulation. Here are just a few of the reasons why.

By using fiber optics to transmit argon laser energy, you get significant improvement in operating freedom. The fiber optics cable is lightweight, flexible and reliable. It replaces heavy, rigid, mirror transmission systems.

Fiber optics also results in delivery instrument flexibility. You can now choose the delivery technique best suited to your particular needs, whether it be a slit lamp; a direct viewing, hand-held ophthalmoscope; or an erect image, indirect ophthalmoscope. And changing from one to another only takes a few minutes.

You're also concerned with economy. The simple adapter allows you to attach or detach your slit lamp to the laser quickly and accurately. This means that you don't have to purchase an additional slit lamp for permanent dedication to photocoagulation. And most important for economy, our unit is priced at less than $25,000.

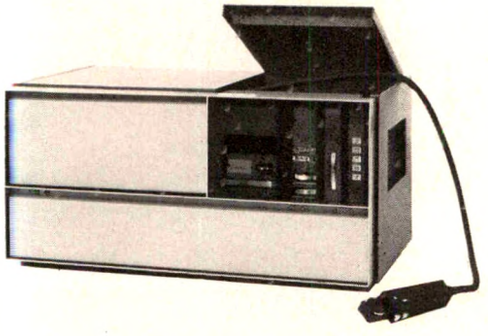
We can't tell you the whole story here, so invest 8¢ in postage and send for the data. And if you're interested in learning more about argon laser photocoagulation, check the box on the coupon. We'll tell you about our regional seminars, clinical discussions to back up your 8¢ investment.

SYNTEX

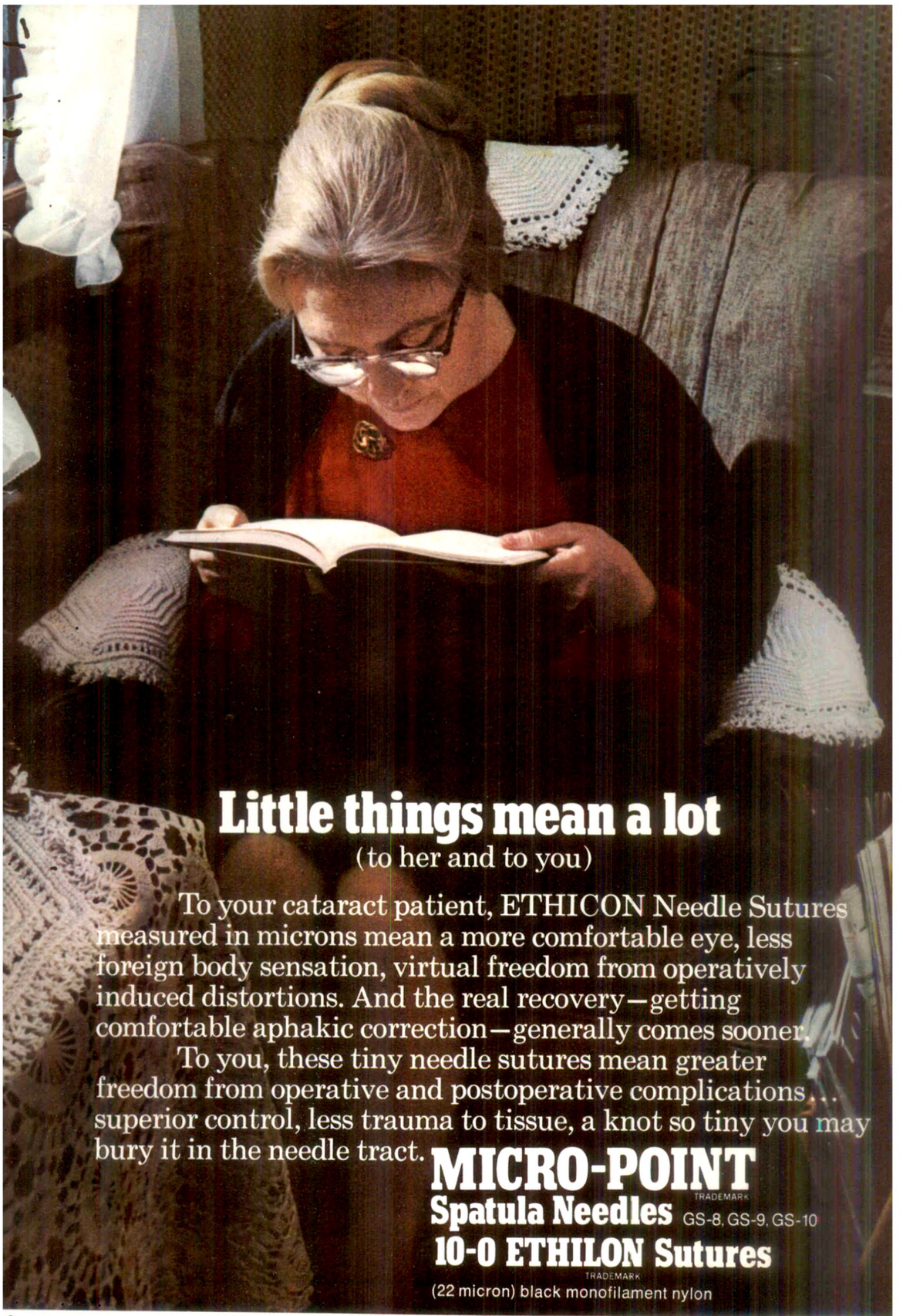
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**Syntex Medical Instruments, Inc.**
3401 Hillview Avenue
Palo Alto, California 94304

Gentlemen:
Please send me
☐ product information about your argon laser photocoagulator.
☐ the details of your scheduled regional seminars.



NAME _____
SPECIALTY _____
HOSPITAL AFFILIATION _____
ADDRESS _____
CITY _____ STATE _____ ZIP _____ TELEPHONE _____



# Little things mean a lot

(to her and to you)

To your cataract patient, ETHICON Needle Sutures measured in microns mean a more comfortable eye, less foreign body sensation, virtual freedom from operatively induced distortions. And the real recovery—getting comfortable aphakic correction—generally comes sooner.

To you, these tiny needle sutures mean greater freedom from operative and postoperative complications... superior control, less trauma to tissue, a knot so tiny you may bury it in the needle tract.

**MICRO-POINT** TRADEMARK
**Spatula Needles** GS-8, GS-9, GS-10
**10-0 ETHILON** TRADEMARK **Sutures**
(22 micron) black monofilament nylon

totally responsible leadership ETHICON

# Little needle, little suture. Little trauma.

A finer mini-suture than has ever before been available, ETHILON 10-0 Monofilament Nylon is made to be left in place indefinitely. Photo shows ETHILON Nylon Sutures in the eye. (MICRO-POINT Spatula Needle GS-10 was used. Arc over eye is a reflection of camera light.)

Photo courtesy of Richard C. Troutman, M.D., F.A.C.S., State University of New York, Downstate Medical Center.

**MICRO-POINT** TRADEMARK
**Spatula Needles** GS-8, GS-9, GS-10
**10-0 ETHILON Sutures** TRADEMARK
(22 micron) black monofilament nylon

Sharper, flatter, smaller, the MICRO-POINT Spatula Needle measures only 0.203 mm., compared to 0.330 mm. for a conventional reverse cutting ophthalmic needle...makes for easier splitting of sclera, minimal trauma.

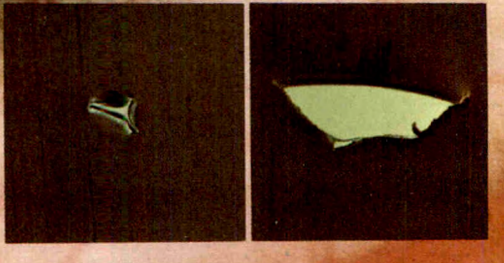


Photo shows the small hole the MICRO-POINT Spatula Needle makes in test material (left), compared to the hole made by conventional reverse cutting needle (right).

totally responsible leadership ETHICON

Specific for
Herpes Simplex Keratitis

**STOXIL®**
**brand of IDOXURIDINE**

the only brand of IDU
available in two forms:
Solution—Ointment

Both now available in Canada




# The choice is yours

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

**Indications:** Only in the treatment of herpes simplex keratitis.

**Description: 'Stoxil' Ophthalmic Solution** contains idoxuridine (5-iodo-2'-deoxyuridine) **0.1% (1 mg./ml.)** in distilled water; sterile when packaged. Preserved with thimerosal, 1:50,000. **'Stoxil' Ophthalmic Ointment** contains idoxuridine **0.5% (5 mg./gram)** in a petrolatum base. (White petrolatum and liquid petrolatum are inactive ingredients.)

**Contraindications:** Contraindicated in patients with known or suspected hypersensitivity to any of its components.

**Precautions:** Some strains of herpes simplex appear to be resistant. If there is no response in *epithelial infections* after 7 or 8 days of treatment, other forms of therapy should be considered.

The recommended frequency and duration of administration should not be exceeded.

'Stoxil' is not effective in corneal inflammations in which the virus is not present.

Corticosteroids are usually contraindicated in herpes simplex keratitis.

Boric acid should not be used during the course of therapy.

'Stoxil' Ophthalmic Solution should not be mixed with other medications.

**Adverse Reactions:** Occasionally, irritation, pain, pruritus, inflammation, edema of the eye or lids and, rarely, allergic reactions have been reported. Photophobia has occurred. Occasionally corneal clouding, stippling and small punctate defects in the corneal epithelium have been observed. The punctate lesions may be a manifestation of the infection.

**How Supplied:** 0.1% Ophthalmic Solution (1 mg./ml.), in 15 ml. bottles with dropper; 0.5% Ophthalmic Ointment (5 mg./gram) in 4 gram tubes.

**Stability:** The Solution should be stored in refrigerator until dispensed. The Ointment does not require refrigeration.

SK&F Smith Kline & French Laboratories

# Midnight Oil



## Something special from Armorlite!

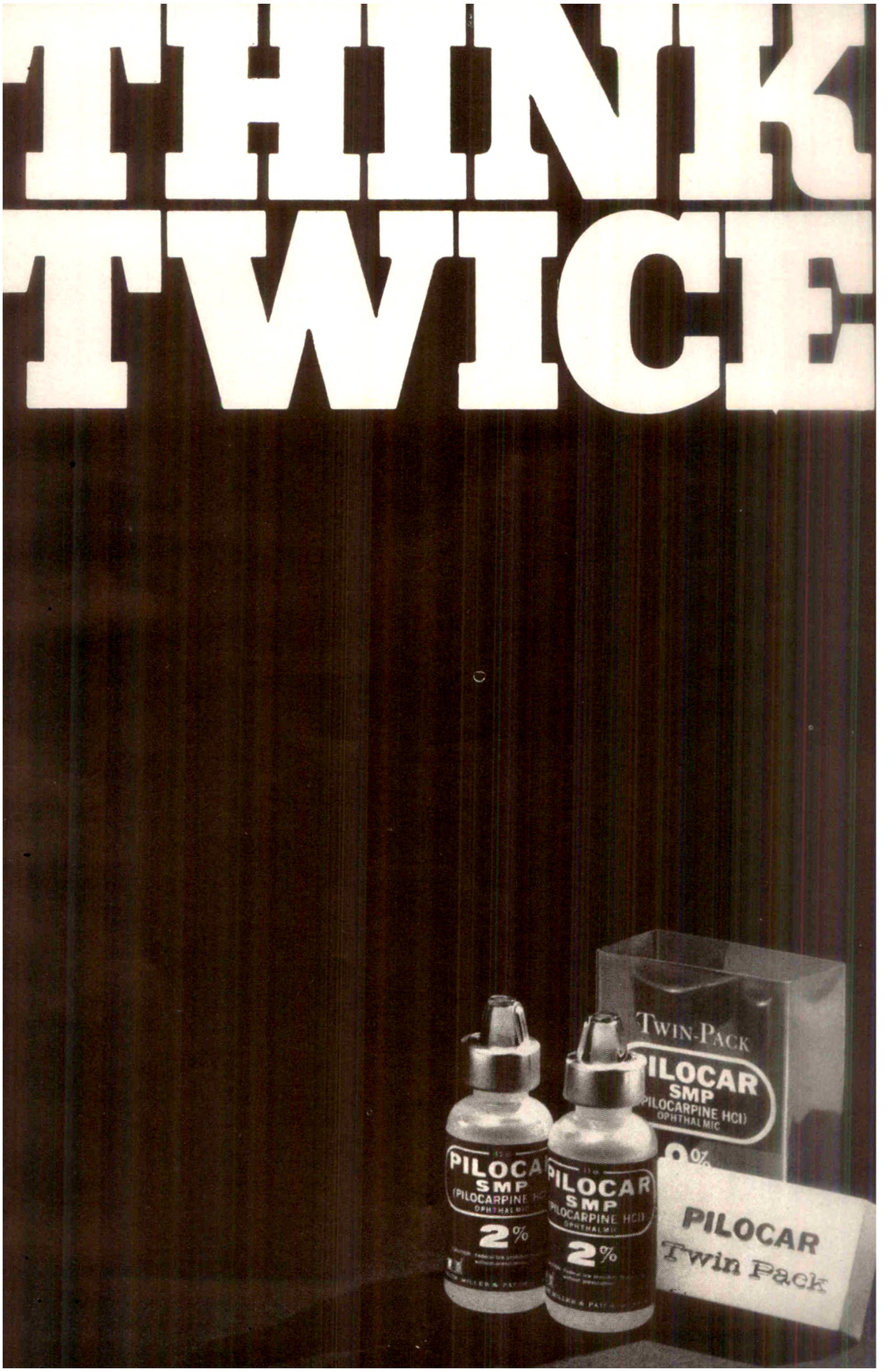
*From the time we introduced our flat-top trifocals, they were so successful, that we could not keep up with the demands. It has taken us years to catch up, but we finally made it.*

*These are the finest hard resin trifocals that money and care can produce. So, when your patient needs the intermediate range of our popular flat-top (or old style round) trifocal, our distributors will have the required lenses in stock.*

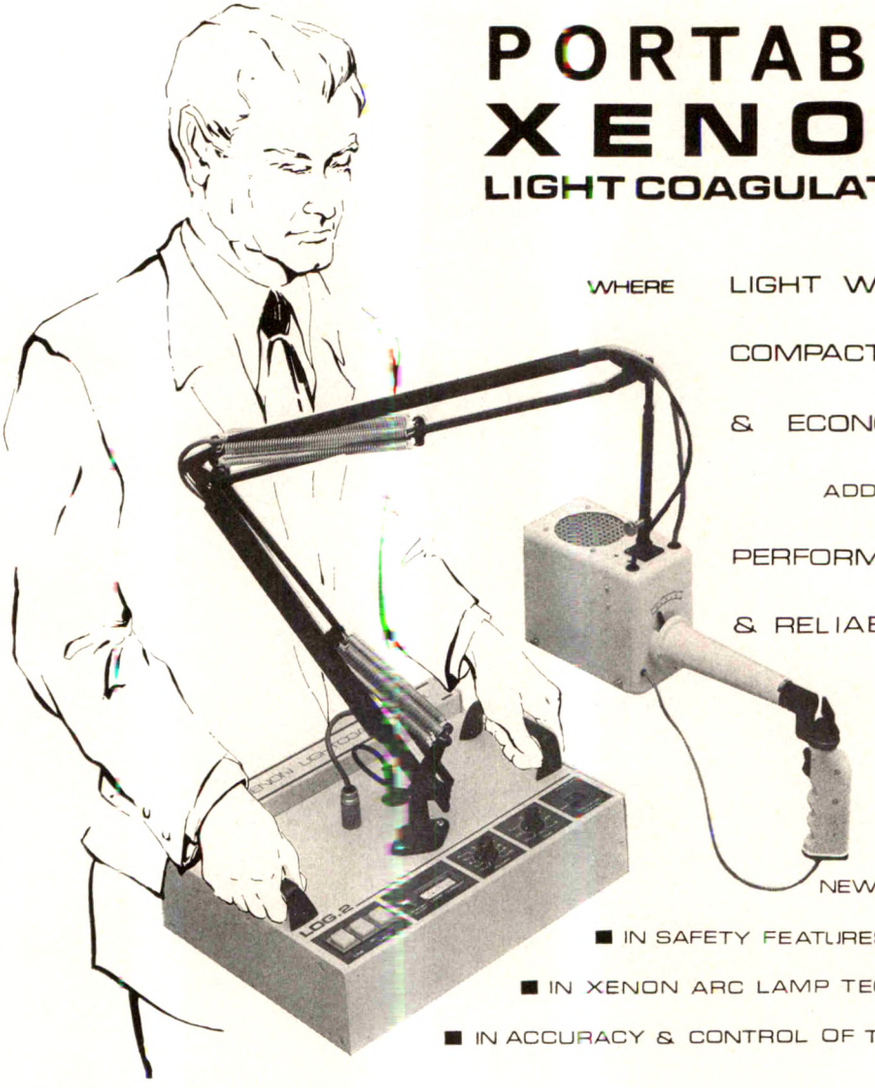
*We won't back order them anymore, but we will keep our lamp handy . . . just to remind us what it's like when we get behind in production.*

**ARMORLITE • INC •**

THE ORIGINATORS OF HARD RESIN LENSES


THINK
TWICE
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2%
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FOR THE OFFICE, OUTPATIENT DEPT. OR SURGERY SUITE.



# PORTABLE XENON LIGHT COAGULATOR

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"to make it perfectly clear–"

# Neosporin®

## Ophthalmic Solution, Sterile

polymyxin B–neomycin–gramicidin

Each cc. contains: Aerosporin® brand Polymyxin B Sulfate 5000 units; Neomycin Sulfate 2.5 mg. (equivalent to 1.75 mg. of neomycin base); Gramicidin 0.025 mg., in aqueous saline solution isotonic with tears, containing the inactive ingredients alcohol (0.5%), propylene glycol, polyoxyethylene polyoxypropylene compound, sodium chloride, and purified water (preservative: thimerosal 0.001%). Bottles of 10 cc. with sterile dropper.

## eradicates bacterial conjunctivitis and other eye infections due to susceptible organisms–

- highly effective against almost all pathogens which invade the eye, including *Pseudomonas* and *Staphylococcus aureus*
- bacterial resistance rarely develops on repeated or prolonged use
- low allergenicity
- also available: Neosporin® Ophthalmic Ointment—Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5000 units; Zinc Bacitracin 400 units; Neomycin Sulfate 5 mg. (equivalent to 3.5 mg. neomycin base) in special white petrolatum q.s. In ⅛ oz. tubes with ophthalmic tip.

*Precaution:* As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

*Contraindications:* This product is contraindicated for subconjunctival or intraocular injection, or for irrigation of fistulous tracts. This product is also contraindicated in those individuals who have shown hypersensitivity to any of its components.

Complete literature available on request from Professional Services Dept. PML.

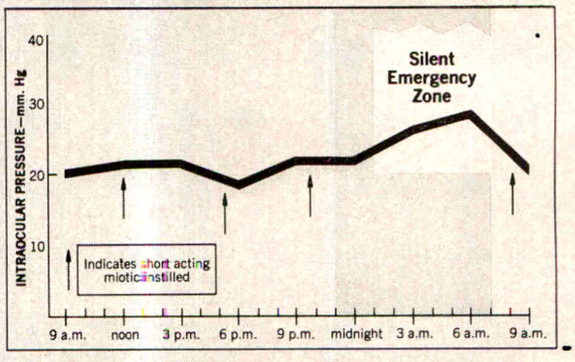
Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

# Not more potent, but longer acting...*

PHOSPHOLINE IODIDE 0.03% and 0.06% were compared with pilocarpine 2% in a study of the time course of changes in outflow facility and intraocular pressure after single dose administration in patients with open-angle glaucoma. While Phospholine Iodide 0.06% showed little diminution in effect on intraocular pressure after 24 hours, the effect of pilocarpine 2% declined markedly in the first few hours, and was almost completely dissipated after 24 hours. The action of Phospholine Iodide 0.03% was intermediate between that of pilocarpine 2% and Phospholine Iodide 0.06%.

## An important consideration in the management of glaucoma

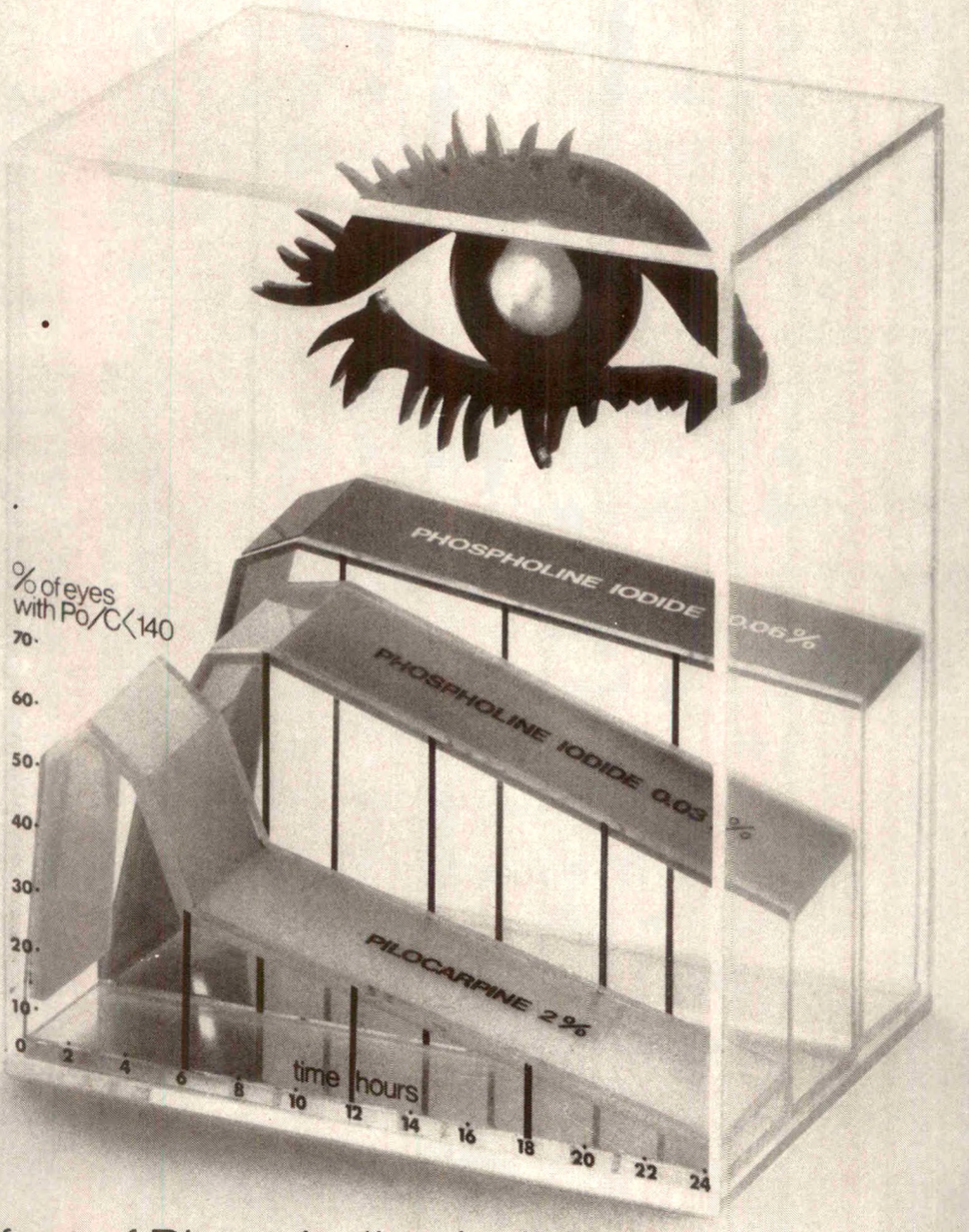



When treated with short acting miotics, the patient with open-angle glaucoma runs the risk of an undetected intraocular pressure buildup during the night—a "silent emergency."

The longer acting Phospholine Iodide® (echothiophate iodide) may protect against this nightly insult. A single instillation of the 0.03% or 0.06% strength before retiring will act through the critical hours, and is especially recommended when you have found pilocarpine to be inadequate.

When initiating therapy... Phospholine Iodide 0.03% can often maintain 24 hour control of intraocular pressure with a single instillation at bedtime. It provides a smooth transition to the higher strengths—0.06%, 0.125%, 0.25% —when necessary. When indicated, epinephrine or carbonic anhydrase inhibitors may be prescribed with any strength of Phospholine Iodide.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide for ophthalmic solution)




Effect of Phospholine Iodide and pilocarpine on intraocular pressure control.

*Adapted from Barsam, P. C., Boston U. School of Med.: Time Curves of the Effect of Miotics on Intraocular Pressure and Outflow Facility, Scientific Exhibit, Annual Convention, American Academy of Ophthalmology and Otolaryngology, Las Vegas, Oct. 5-9, 1970.

See next page for Brief Summary of prescribing information.

# PHOSPHOLINE IODIDE®
## (echothiophate iodide)

for 24 hour control in chronic simple (open-angle) glaucoma and glaucoma secondary to aphakia

just 1 or 2 instillations a day
- for long lasting effect on ocular tension—
helps protect against a "silent emergency" at night
- may be substituted for the bedtime dose of a short acting miotic
that controls intraocular pressure by day, but
fails to provide adequate control during the night and early morning
- choice of four strengths for individualized therapy—
may be used alone or as a complementary agent

**BRIEF SUMMARY (for full prescribing information, consult package circular)**
**Phospholine Iodide® (echothiophate iodide)**
**In Management of Chronic Simple (Noncongestive) and Aphakic Glaucoma/Concomitant Esotropia**

**Contraindications:** This medication is contraindicated in acute (congestive) angle closure glaucoma, but may be useful in the subacute or chronic stages after iridectomy or where surgery is refused or contraindicated. It is also contraindicated in glaucoma associated with iridocyclitis. It should be prescribed only after consultation with the patient's internist or surgeon in the presence of bronchial asthma, gastrointestinal spasm, urinary tract obstruction, vascular hypertension, myocardial infarction, and Parkinson's disease.

**Warnings:** Therapy should be temporarily discontinued if (otherwise unexplainable) persistent diarrhea, profuse sweating, or muscle weakness occurs. Succinylcholine should not be used concomitantly. In patients with myasthenia gravis, only specialists who are aware of the likelihood of drug interactions should employ PHOSPHOLINE IODIDE (echothiophate iodide) concomitantly with neostigmine, ambenonium, pyridostigmine, or edrophonium.

**Use in pregnancy:** Not established is safe use in pregnancy, nor absence of adverse effects on fetus or on respiration of neonate. Administration in pregnancy requires weighing potential benefits against potential hazards.

**Precautions:** Patients regularly exposed to pesticides of the organophosphate or carbamate class should be cautioned to observe all protective measures recommended in their handling.

**Minor side effects** *(patient to be alerted):* Initially, browache, dimness of vision, blurring, or ciliary and conjunctival injection may occur, but usually disappear after 5 to 10 days of treatment.

**Other side effects:** *(local)* Iris cysts occur occasionally in adults, but fairly frequently in children. Pigmented cysts of the ciliary epithelium have been noted. Retinal detachment has occurred, and the medication should be used with extreme caution, if at all, if there is a history of this disorder. It may cause or activate acute iritis. Posterior synechiae may develop. Recent controlled clinical studies have shown that PHOSPHOLINE IODIDE (echothiophate iodide) therapy may be a causative factor in the development of lens opacities in adult glaucoma patients. This phenomenon is apparently (a) *dose-related,* since it has not been observed with 0.03%, but only with the higher strengths; (b) *selective in character,* since some patients have tolerated many years of treatment with the highest strength of the drug without lens changes; (c) *age-related,* since lens opacities associated with this medication are virtually unknown in children; and (d) *species specific,* since attempts to produce comparable effects in experimental animals have been unsuccessful. Pupillary block may develop due to intense miosis together with vascular congestion, especially in eyes with narrow angles.

Resistance to the medication may appear in some patients after many months of therapy; usually the response can be restored by changing to another medication for a short time.

*(systemic)* Rarely, systemic effects may appear such as gastrointestinal spasm, nausea, vomiting, diarrhea, increased secretion of lacrimal, salivary or sweat glands, tightness in the chest, bradycardia, etc. Muscle weakness and one case of localized paresthesias have been reported. Lowering of blood cholinesterase level frequently occurs during long term therapy and is an indication of systemic absorption, not an adverse side effect.

**Antidotes:** Atropine, 2 mg. parenterally; PROTOPAM® CHLORIDE (pralidoxime chloride), 25 mg./Kg., I.V.; artificial respiration, if necessary.

**Supplied:** 1.5 mg. package for dispensing 0.03% solution; 3.0 mg. package for 0.06% solution; 6.25 mg. package for 0.125% solution; 12.5 mg. package for 0.25% solution. [Also contains potassium acetate (sodium hydroxide or acetic acid may have been incorporated to adjust pH during manufacturing), chlorobutanol (chloral derivative), mannitol, boric acid, and exsiccated sodium phosphate.]

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

# A little innovation is a big help

**Nothing is quite as satisfying as finding a new way to help the patient.**

**You will help a beginning presbyope** adjust to his bifocal correction by simply adding Press-On™ lenses to his present single vision spectacles. The interim Press-On lenses establish usefulness and acceptance. Also, they will help determine the proper seg height, shape and size before the permanent Rx is produced.

**Reading aids for low vision patients** have been a real problem. Adds above +3.00 have been impractical for everybody concerned. Press-On lenses give you bifocal segments of any size and shape incorporating proper prism to insure comfortable binocular vision. They can be applied in minutes.

**Post-operative cataract patients** are apprehensive. Wouldn't it be a happy innovation to hand these patients their own comfortable glasses with an interim aspheric Press-On lens correction that provides a panoramic field of view. They will see better and look better, immediately.

These are a few examples. Clip the coupon, and we'll send you more ideas plus a Press-On lens for your own use.

All OSG Fresnel lenses provide optimum asphericity regardless of power.

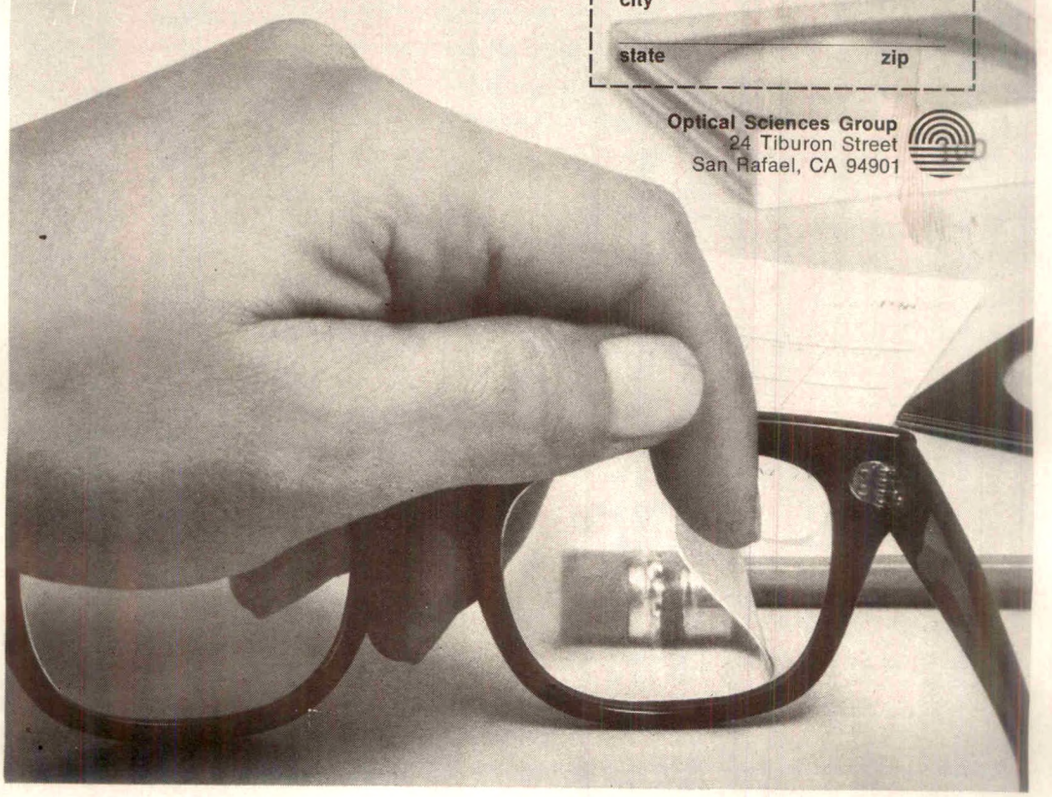
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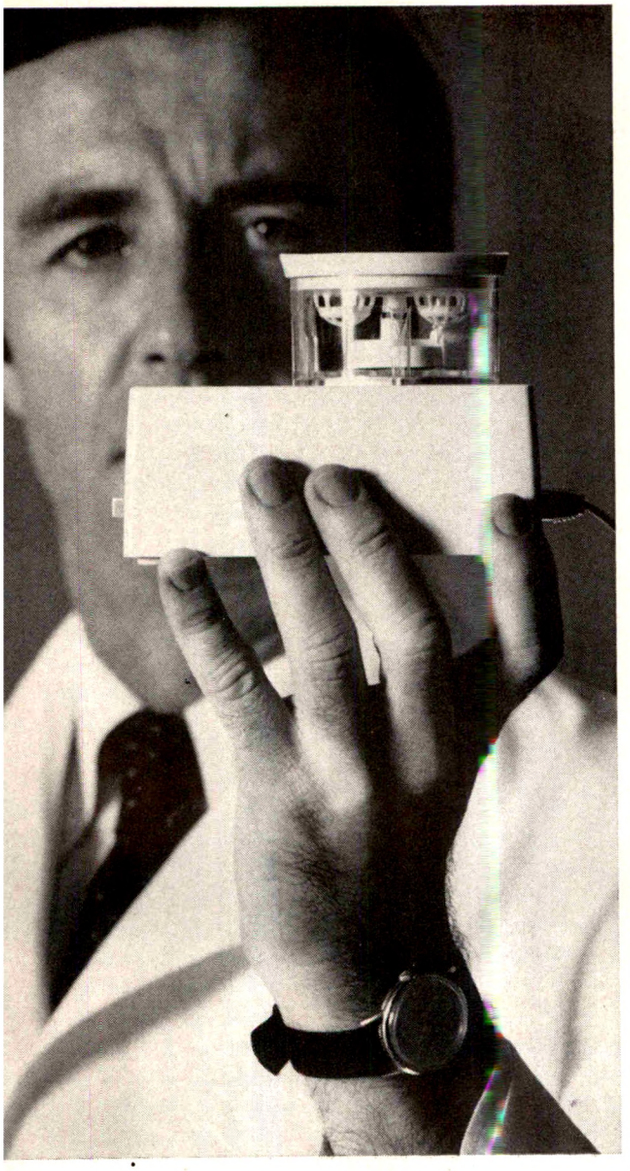
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**Optical Sciences Group**
24 Tiburon Street
San Rafael, CA 94901



# Introducing
# SWIRL CLEAN™
## electric contact lens cleaner by Contique™

## the professional way to clean contact lenses



Until now, the most common method cleaning contact lenses has been to rub the between the fingers. As you know, this syste has three serious drawbacks: 1) it doesn't clea properly; 2) it *can* scratch or warp lenses; 3) may not be sanitary.

### A new, more efficient technique

The new Swirl Clean electric contact le cleaner by Contique approaches the problem a totally different manner: It combines th cleaning power of a high-speed agitator wi the detergent action of Contique Cleaning Sol tion. The result is thorough but gentle clea ing—with a minimum of handling and le chance of lens loss.

Swirl Clean doesn't stop there. It provid a convenient place to soak and store lenses b tween wearings.

### Perfect for office use

How many times have you wished for ju such an efficient way to clean your patien contacts—when you are delivering a new p or after making an adjustment?

Swirl Clean fills this long-felt need p fectly. It's compact. Easy to use. And it *loo* highly professional. Your patients can s you've gone to the expense of securing the m advanced cleaning device available to ma sure their lenses are clean and comfortable.

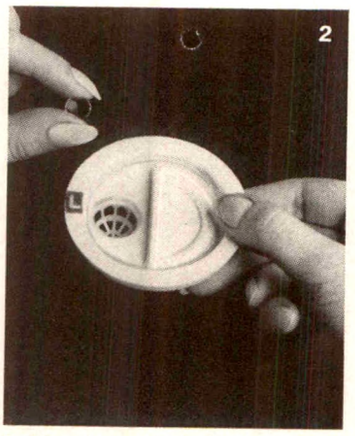
And it takes only a few seconds to cle contacts with the Swirl Clean. Once you get in the habit, you'll wonder how you managed wi out it.

### Your patients will want one, too

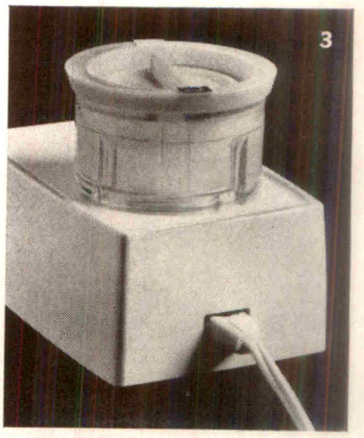
When they see how effortlessly you cle their contacts with the Swirl Clean, your n contact lens wearers will want one of their o to use at home. That's why it makes good bu ness sense to stock a few units to sell or reco mend to your patients. They'll never be m psychologically receptive than at the mom



*Fill cleaning chamber ¾ full with old water. Add 6-8 drops of Contique Cleaning Solution and place on base.*



**2** *Place lenses in bottom of clearly marked LEFT and RIGHT baskets of lens holder. Close lid. Place lens holder on cleaning chamber.*



**3** *Flip "ON" switch and run Swirl Clean 30-60 seconds. You can see the lenses being swirled clean before your eyes.*

hey get their new contacts. It's also a good way of starting them off on a proper lens-care regimen and helping them become satisfied wearers.

### Read what Swirl Clean users say

• An O.D. in Knoxville, Tenn. writes: "The compactness of this unit makes its use a pleasure in my office." An M.D. in Bakersfield, Calif. calls Swirl Clean "a very valuable asset to our office." An optician in Long Beach, Calif.: "Excellent method of cleaning lenses after lab adjustment."

Enthusiastic comments have also come in from contact lens wearers all over the country. "My vision is so much better with clean contacts." (Boston, Pa.) "I enjoy its convenience and notice my lenses are more comfortable." (East Point, Ga.) "Cleans lenses 100% better than by hand." (Hyde Park, Mass.) "I wear lenses 16 hours a day and find their comfort greatly increased." (Indianapolis, Ind.)

These comments are on file at Alcon Laboratories and may be examined by anyone interested.




### Complete lens care by Contique

Used with the new Swirl Clean, *Contique Cleaning Solution* dissolves eye-irritating deposits such as mucus, oil and film. Yet it's so gentle you can recommend it with complete confidence. *Contique Soaking Solution* "conditions" lenses by keeping them chemically moist when stored in the special Swirl Clean soaking dish, increasing wettability and wearing comfort. *Contique Wetting Solution* creates a liquid cushion between lens and eyes, makes placement smooth and easy, and can also be used to re-wet lenses during the day.

This family of lens care products from Contique can help your patients become successful, satisfied contact lens wearers. Almost $6 worth of Contique solutions are packed with every Swirl Clean at no additional cost. For more information about the new Swirl Clean and other Contique products, call your optical wholesaler today.

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PTICAL PRODUCTS DIVISION, ALCON LABORATORIES, INC., P.O. BOX 1959, FORT WORTH, TEXAS 76101



# Fly now. Pay later.

And he will. Wind, cold and glare on the slopes make for red, watery eyes back at the lodge. If he hasn't got goggles, he should have Vasocon-A. Long-acting vasoconstrictor, decongestant, antihistamine combination. It relieves the burning, itching and watering of windblown eyes. Reduces conjunctival hyperemia in all minor eye irritations. Helps with contact lens insertion and removal, as well. Vasocon-A. It's the only way to fly.

Smith, Miller & Patch, Inc., New York

CAUTION: Federal law prohibits dispensing without prescription. See package insert before prescribing.

COMPOSITION: Naphazoline HCl 0.05%; antazoline, 0.5%; boric acid, 1.2%; sodium carbonate anhydrous; sodium chloride; phenylmercuric acetate (preservative) 0.002%.

SIDE EFFECTS: Except for transitory stinging, side effects have rarely been encountered.

CONTRAINDICATIONS: Should not be used by patients with narrow angle glaucoma. If irritation persists or increases, patient should be advised to discontinue use and return to physician.

SUPPLIED: 15 cc dropper-tip vials.

## Vasocon-A

Smith, Miller & Patch, Inc., New York

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FOR CATARACTS

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ACTUAL SIZE

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ONCE YOU GRASP THE LENS, AT NO TIME DOES THE IRIS OR ANY OTHER TISSUE ADHERE TO THE PROBE, EVEN WHEN THERE IS DIRECT CONTACT!. THIS EXCEPTIONAL ADVANTAGE IS DUE TO ITS SPECIALLY DESIGNED TIP.

OTHER IMPORTANT ADVANTAGES

- Thin tip (2.75 mm.) with special shape for better visibility.
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- Durable, it can be used a great number of times.
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Ref. : Covelli B. Am. J. Ophth., 69:3, 1970
Presented at the VII Pan-Am. Congr. Ophth., Bogota, 1971

*Reg'd Trademark E. I. DuPont

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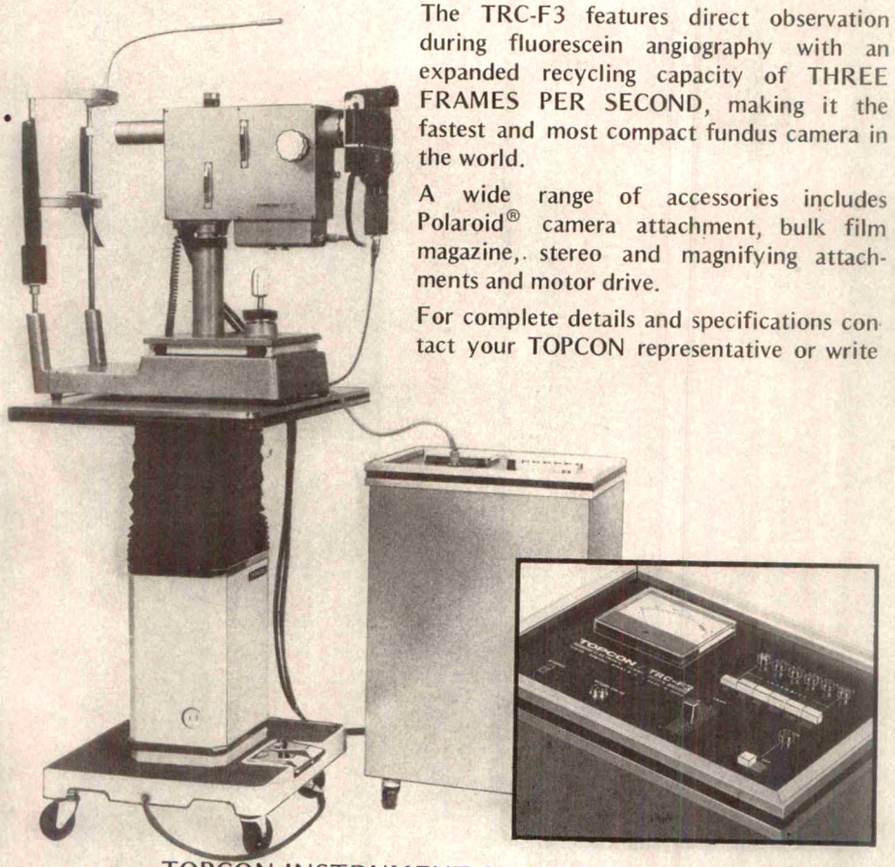
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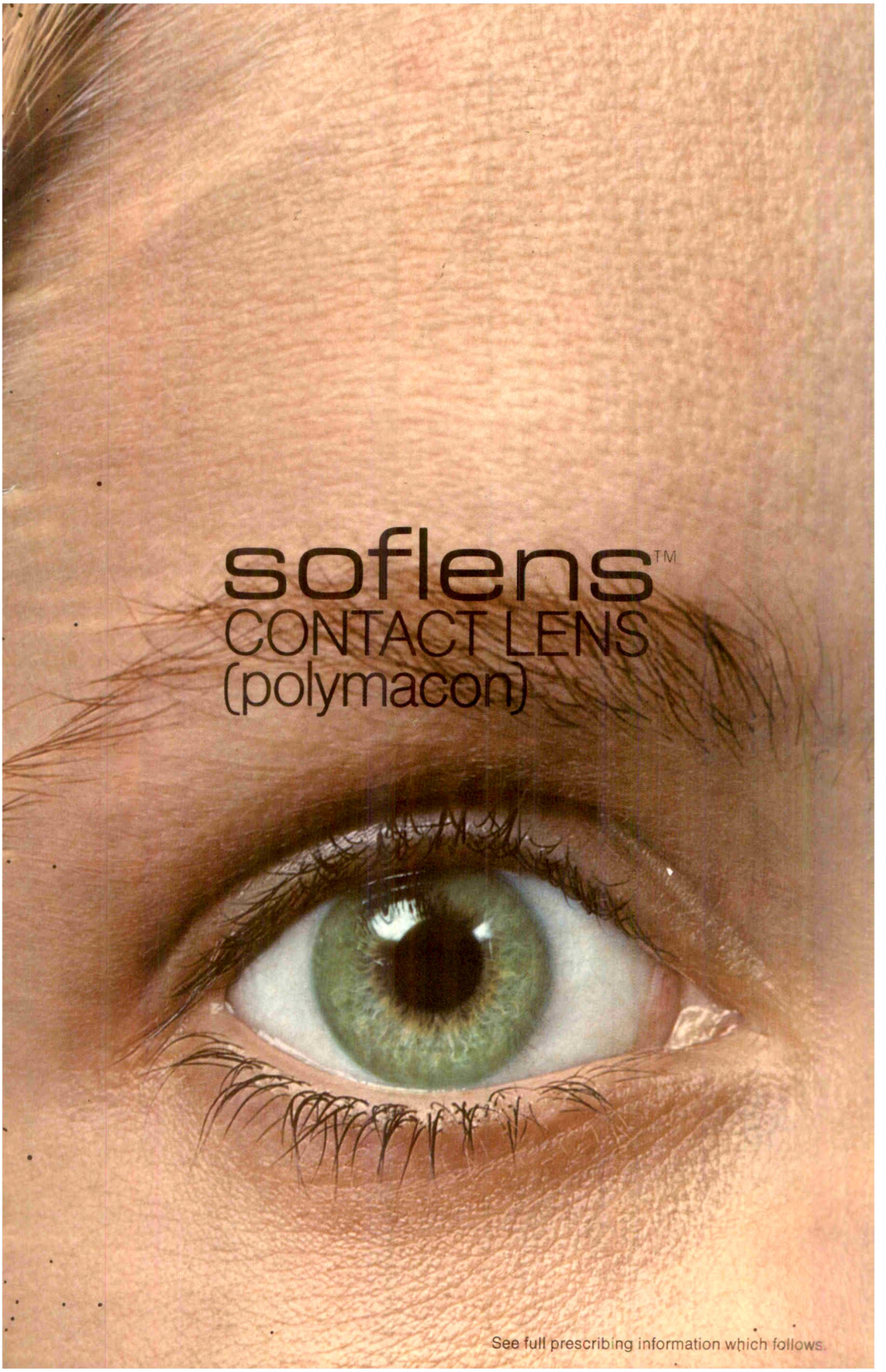
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soflens™
CONTACT LENS
(polymacon)
See full prescribing information which follows.




Conventional methods of fitting contact lenses do not apply to SOFLENS Contact Lenses (polymacon). For a detailed description of the fitting technique, refer to the SOFLENS Fitting Guide, copies of which are available from: SOFLENS Division, Bausch & Lomb Incorporated, Rochester, New York 14602.

**DESCRIPTION:** The SOFLENS Contact Lens (polymacon) is a hemispherical shell of approximately 13mm chord diameter and 0.1 to 1.0mm thickness. It consists of 61.4% poly (2-hydroxyethyl methacrylate) and 38.6% water by weight when immersed in normal saline. The SOFLENS Care Kit is a package required for lens asepticizing, cleaning, and storage consisting of the following:

| | |
|---|---|
| SOFLENS Carrying Case | Cat. #140301 |
| SOFLENS Aseptor-Patient Unit | Cat. #140302 |
| SOFLENS Squeeze Bottle | Cat. #140304 |
| SOFLENS Salt Tablets | Cat. #140305 |
| SOFLENS Patient Instruction Book | Cat. #140300-100 |

**ACTIONS:** The SOFLENS Contact Lens (polymacon) absorbs water to 38.6% of its dry weight when equilibrated in normal saline solution. In its hydrated state a SOFLENS Contact Lens (polymacon) becomes soft and pliable. When placed on the human cornea the hydrated SOFLENS Contact Lens (polymacon) acts as a refracting medium to compensate spherical ametropias. The material has a refractive index of 1.43 and the lens has a visible light transmittance greater than 97%.

**INDICATIONS:** SOFLENS Contact Lenses (polymacon) are indicated for the correction of visual acuity in persons with non-diseased eyes who have spherical ametropias; refractive astigmatism of 1.50 diopters or less and/or corneal astigmatism of 2.00 diopters or less.

**CONTRAINDICATIONS:** SOFLENS Contact Lenses (polymacon) are contraindicated by the presence of any of the following conditions. (1) Acute and subacute inflammations of the anterior segment of the eye. (2) Any eye disease which affects the cornea or conjunctiva. (3) Insufficiency of lacrimal secretion. (4) Corneal hypoesthesia. (5) Any systemic disease which may affect the eye or be exaggerated by wearing contact lenses. (6) Early stages of pregnancy.

**WARNINGS: Medicants and Eye Drops**—SOFLENS Contact Lens (polymacon) must be stored ONLY in normal saline solution. No ophthalmic solutions or medicants, including conventional contact lens solutions, can be used by SOFLENS Contact Lens (polymacon) wearers prior to or while the lens is in place on the eye. Also, no solutions, including conventional contact lens solutions, other than normal saline may be used on SOFLENS when the lens is off the eye.

**Abrasions and Infections**—If the lenses become less comfortable to the wearer than when they were first placed on the wearer's corneas, this may indicate the presence of a foreign body. The lens should be removed immediately and the patient examined. If any eye abrasion, ulceration, irritation or infection is present, a physician should be consulted immediately.

**Wearing Restrictions**—SOFLENS Contact Lenses (polymacon) should be removed before sleeping or swimming and in the presence of noxious and irritating vapors.

**Visual Blurring**—When visual blurring occurs the lens must be removed until the condition subsides.

**Lens Sanitation**—Patients who would not or could not adhere to recommended daily sanitary care of SOFLENS Contact Lenses (polymacon) should not be provided with them.

**PRECAUTIONS: Storage**—SOFLENS Contact Lenses (polymacon) must be stored ONLY in normal saline solution. If left exposed to air, the lenses will dehydrate, become brittle, and break readily. If a lens dehydrates, it should be soaked in normal saline solution until it returns to a soft, supple state.

**Cleaning and Asepticizing**—SOFLENS Contact Lenses (polymacon) must be BOTH cleaned and asepticized daily. One procedure does not replace the other. CLEANING is necessary to remove mucus and film from the lens surface. ASEPTICIZING with the SOFLENS Aseptor-Patient Unit has been shown to prevent the growth of certain organisms, namely Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Candida albicans, and Herpes simplex, on the lens and in the SOFLENS Carrying Case. Fresh normal saline must be prepared daily for cleaning and storing the lenses. The carrying case must be emptied and refilled with fresh normal saline solution just before asepticizing the lenses. If a SOFLENS Aseptor-Patient Unit is not available for asepticizing the lenses, the lenses must be boiled in their carrying case in a pan of water for 15 minutes.

**Hygiene**—Hands must be washed, rinsed thoroughly, and dried with a lint-free towel before handling the lenses. Cosmetics, lotions, soaps, and creams must not come in contact with the lenses since eye irritation may result. If hair spray is used while the lenses are being worn, the eyes must be kept closed until the hair spray has settled.

**Fluorescein**—Never use fluorescein while the patient is wearing the lenses because the lenses will become discolored. Whenever fluorescein is used, flush the eyes with normal saline solution and wait at least one hour before replacing the lenses. Too early replacement may allow the lenses to absorb residual fluorescein irreversibly.

**ADVERSE REACTIONS:** Serious corneal damage may result from wearing a lens which has been soaked in a conventional contact lens solution containing preservatives. Eye irritation may occur within a short time after putting on a hypertonic lens. Removal of the lens will relieve the irritation. Very rarely a lens may adhere to an eye as a result of the patient sleeping with the lens on or wearing a hypotonic lens. If a lens adheres for any reason, apply normal saline and wait until the lens moves freely before removing it. Clinical studies indicate visual blurring is experienced by less than 5% of SOFLENS Contact Lens (polymacon) wearers. Rainbows or halos around objects or blurring of the vision may occur if the lenses are worn continuously for too long a time. Removal of the lenses and a rest period of at least one hour generally relieves these symptoms. Excessive tearing, unusual eye secretions, and photophobia are not normal; if these symptoms occur, the patient should be examined to determine their cause.

**DOSAGE AND ADMINISTRATION:** There may be a tendency for the patient to overwear the lenses initially. Therefore, the importance of adhering to the following initial daily wearing schedule should be stressed to the patient:

| Day | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) | Rest Period (hours) | Wear Time (hours) |
|---|---|---|---|---|---|
| 1 | 3 | 1 | 3 | 1 | 3 |
| 2 | 3 | 1 | 3 | 1 | 3 |
| 3 | 4 | 1 | 4 | 1 | 4 |
| 4 | 4 | 1 | 4 | 1 | 4 |
| 5 | 6 | 1 | 6 | 1 | 4 |
| 6 | 6 | 1 | 6 | 1 | 4 |
| 7 | 8 | 1 | 8 | | |
| 8 | 8 | 1 | 8 | | |
| 9 | 8 | 1 | 8 | | |
| 10 | 10 | 1 | balance of the waking hours* | | |
| 11 | 12 | 1 | balance of the waking hours* | | |
| 12 | 14 | 1 | balance of the waking hours* | | |

*Lenses should never be worn 24 hours a day.

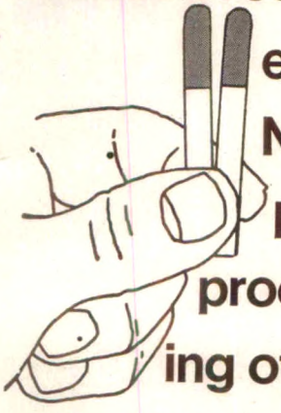
Care must be taken on the initial visit to assure that the patient is supplied with a SOFLENS Care Kit and fully understands all care and handling instructions for the lenses. As with any contact lens, regular recall visits are necessary to assure patient health and compliance with instructions.

**HOW SUPPLIED:** Each lens is supplied sterile in a glass vial containing sterile normal saline solution. The glass vial is marked with the dioptric power (black for plus power lenses; red for minus) and the manufacturing lot number of the lens. To assure proper lens care and handling, each SOFLENS patient must be supplied with a complete SOFLENS Care Kit.

**BAUSCH & LOMB**
SOFLENS DIVISION

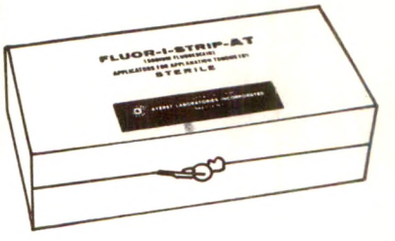


**When fitting contact lenses: to guard against the risk of infection inherent in the use of sodium fluorescein solutions, stain eyes with sterile Fluor-I-Strip-A.T. No excess fluorescein to stain the patient's face or clothing...water-proof grip to prevent staining of your fingers. Simply retract upper lid, apply dry orange tip of flexible applicator to the bulbar conjunctiva at the temporal side. For all these benefits: Specify Ayerst**





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**STERILE OPHTHALMIC APPLICATORS.**




*Each applicator contains* not less than 1.0 mg. sodium fluorescein—provided by precise impregnation with a solution of sodium fluorescein and 0.5% chlorobutanol (chloral derivative), polysorbate 80, boric acid, potassium chloride, and sodium carbonate. *Supplied:* No. 1048—Boxes of 100 envelopes, each envelope containing 2 firm sterile applicators—one for each eye.

OPHTHALMOS DIVISION

The Ophthalmos Division
AYERST LABORATORIES
New York, N.Y. 10017

7047

**Composition:**

**Inflamase**

*Prednisolone Sodium Phosphate .....0.125%
(Equivalent to Prednisolone 0.1%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

**Inflamase Forte**

*Prednisolone Sodium Phosphate 1.0%
(Equivalent to Prednisolone 0.8%)
Benzalkonium chloride .....0.01%

In an aqueous buffered isotonic solution containing disodium ethylenediaminetetraacetate, mono and dibasic sodium phosphate, and sodium chloride.

Prednisolone Sodium Phosphate is a water soluble inorganic ester of prednisolone. It is approximately 2,000 times as soluble in water at 25°C. as is hydrocortisone.

*Licensed under patent #3,134,718.

**Indications:** Inflamase and Inflamase Forte ophthalmic solutions may be used effectively in the following conditions of the anterior segment of the eye: superficial keratitis, including punctate epithelial lesions (Thygeson type), phlyctenular keratoconjunctivitis, and Sjogren's keratoconjunctivitis (with systemic steroids); deep keratitis, including interstitial or parenchymatous keratitis, acne rosacea, sclerosing keratitis; herpes zoster opthalmicus (do not use in herpes simplex); non-purulent conjunctivitis, including vernal, allergic, catarrhal; iridocyclitis; acute iritis; recurrent marginal ulceration, whether endogenous or due to atopic or contact allergies, or microbial allergy; corneal injuries, such as aseptic thermal, radiation, or chemical burns and corneal injuries following surgery or the penetration of foreign bodies; lid allergy; and non-purulent blepheritis, including catarrhal and allergic.

Inflamase and Inflamase Forte ophthalmic solutions have their principal effect on the anterior segment of the eye (cornea and the anterior uvea), with acute disorders responding more favorably than chronic disorders. Inflamase Forte 1% solution is recommended for moderate to severe inflammations particularly when rapid control is desired. In stubborn cases of anterior segment eye disease, systemic adrenocortical hormone therapy may be required. When the deeper ocular structures are involved, systemic therapy is necessary.

**Dosage:** Initially, 1 or 2 drops placed in conjunctival sac every hour during day and every 2 hours during night until improvement occurs. Thereafter, 1 or 2 drops 2 to 4 times daily.

**Contraindications:** Contraindicated in acute herpes simplex, ocular tuberculosis, vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva; fungal diseases of the eye. Purulent conjunctivitis, purulent blepharitis, and infectious conditions are contraindications to the use of steroids.

**Side Effects:** Extended use of topical steroid therapy may cause increased intraocular pressure in certain individuals. It is advisable that intraocular pressure be checked frequently. In those diseases causing thinning of the cornea, perforation has been known to occur with the use of topical steroids.

**Warning:** If irritation persists or develops, patient should be advised to discontinue use and consult prescribing physician.

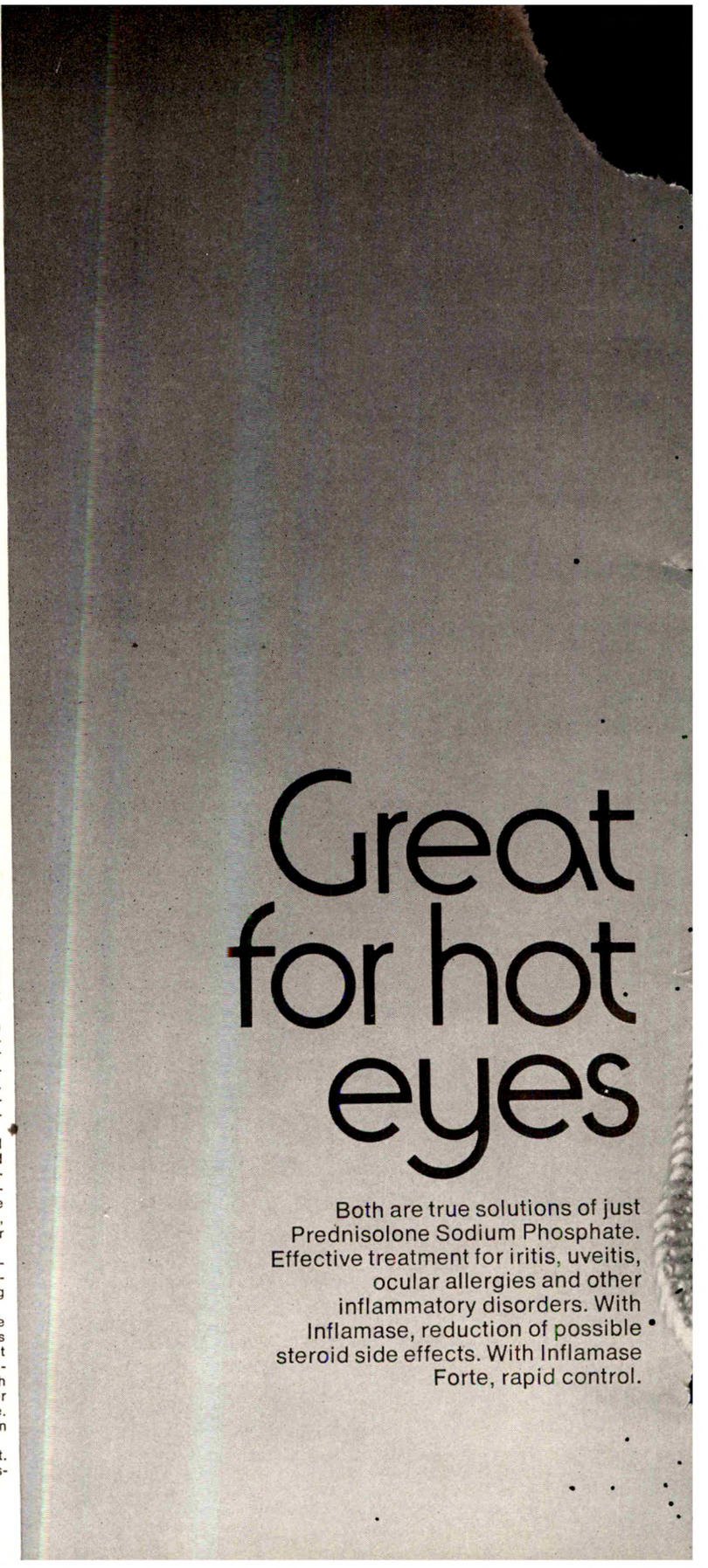
**How Supplied:** 5 cc plastic squeeze bottle with dropper tip. These products are sterile when packaged. To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area, or other areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Store in cool place. Protect from light.

**Caution:** Federal law prohibits dispensing without prescription.

**Smith, Miller & Patch, Inc.**

401 Joyce Kilmer Avenue
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# Great for hot eyes

Both are true solutions of just Prednisolone Sodium Phosphate. Effective treatment for iritis, uveitis, ocular allergies and other inflammatory disorders. With Inflamase, reduction of possible steroid side effects. With Inflamase Forte, rapid control.




**Inflamase**
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**Inflamase Forte**
for the tough ones.

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Younger Seamless Lenses are invisible *true* bifocals, not lenses with a "blended" power that may introduce undesirable lateral astigmatism. Vision through the distance portion is sharp and clear, through the center or laterally. The same is true of the reading area.

Youngers are *cosmetic* lenses, not cure-alls.

If the patient needs the three fields of a trifocal for efficient vision, however, even Younger Lenses won't help. In this case, prescribe the *finest quality trifocal* you can order. There is no substitute for trifocals when indicated, and the patient is entitled to the best you can provide.

**NO FITTING PROBLEMS, NO LAB PROBLEMS with Younger Seamless Lenses! Immediate service from most independent labs and American Optical branches . . . in glass or hard resin!**

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# CONTACT LENSES AND THE APHAKIC PATIENT

## Part 4: Fitting Considerations

Aphakic lenses, like all corneal contact lenses, can be satisfactorily fitted in a wide range of sizes, provided that the other variables are adjusted accordingly. The smaller the diameter, the "looser" the lens, thus, for sufficient adhesion, it must be made steeper, thinner, and/or with a larger optical zone. Conversely, a large lens tends to be "tight"; thus, to avoid interference with tear interchange, we can compensate by making it flatter, thicker, and/or with a smaller optical zone. Occasionally, a large diameter lens may even require auxiliary venting, using apertures or channels.

The practitioner accustomed to fitting conventional diameter lenses (9.0 mm to 9.8 mm) can compensate for the extra weight of aphakic lenses in one of two ways:

(1) Order base curves one-half diopter steeper than usual, all other specifications being the same (except thickness).

(2) Order diameters .4 mm to .6 mm larger than usual, all other specifications being the same (except thickness).

Either way, the MINUS-CARRIER LENTICULAR LENS should be used when dealing with a keyhole pupil and some upper lid cover, or with a low lower lid. The TP (TANGENTIAL PERIPHERY) LENS is preferred when the patient has a small, round pupil, especially in conjunction with a tight upper lid.

Turning now to small lens fitting: Good results with aphakics depend on reducing lens weight to a minimum. This is best achieved with the MINUS-CARRIER LENTICULAR LENS made with a small (preferably 7.0 mm) anterior optical zone. The base curve should be 0.25 to 0.50 D. steeper than usual for a small thin lens of the same diameter (see my monograph "Small, Thin Contact Lenses," page 4, table II). If the LENTICULAR LENS does not center properly due to lid effects, then a TP (TANGENTIAL PERIPHERY) LENS should be tried, made to the same specifications (except that the thickness will be about .10 mm greater due to the tangential design).

In cases of "against the rule" corneal astigmatism of more than 2.00 D., if proper centering is not attainable with spherical lenses, then inside toric lenses should be considered. In cases where the effective pupil size is too large for coverage by a LENTICULAR LENS, we can sometimes use a small SINGLE-CUT LENS made without peripheral curves (lens diameter = optical zone) so that the entire lens is optimally functional. It should always be borne in mind that small lenses must have more perfect centering than other types; otherwise, they cannot be used successfully.

STANLEY GORDON, *President*

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## Tillyer Topics



E. WILLIAM TILLYER

# Photochromic glass

In recent years, photochromic glass lenses have become extremely popular. A review of this material's characteristics and ways of handling it seem appropriate at this time.

Briefly, photochromic glasses are those glasses whose transmissions are changed by the increase or decrease of broad or narrow bands of light emission. In our industry, the most widely recognized glass is Photogray® glass made by Corning Glass Works.

In Photogray glass, silver halides are buried within the glass. These halides darken when exposed to ultraviolet light. When the ultraviolet source is removed, the halides gradually fade and the glass returns to a lighter shade.

Ultraviolet light is the only light transmission that causes the on-off effect. Photogray glass does not absorb infrared heat rays. In fact, infrared transmission (heat) somewhat inhibits the effect. When exposed to direct sunlight at 77°F., transmittance drops to 45%. When exposed to sunlight at 34°F., transmittance drops to 34%. This is the reason why Photogray glass acts faster, and more completely, on cold sunny days than it does on hot sunny days.

Before being exposed to ultraviolet, Photogray lenses have a slightly greenish hue. After exposure—and removal from the exposure—Photogray lenses return to a pinkish color (similar to our Cruxite® AX lenses). Transmission is about 85%.

That is why a new prescription lens does not match a lens which has undergone several exposures. And why we recommend pre-exposure to sunlight, or other ultraviolet source, before giving a replacement lens to the patient. Exposing the lens several times usually produces an excellent match.

Photogray lenses do not darken appreciably when worn while driving. The automobile windshield and windows cut out most of the ultraviolet rays in the area where Photogray is activated.

Photogray lenses can be heat treated on standard machines, provided the proper time/temperature tables are used. But they will not activate completely unless you closely follow the tables. Reducing the heat and time below the recommended limits may curtail the activity of the glass.

We have had some success with colored metallic oxide vacuum coatings (Ultracoat) on the rear surface. This slightly reduces the range of activation but provides a darker lens to start with.

Photogray lenses cannot be fused and fused bifocals are not available. However, this shouldn't cause problems because the one-piece Executive® bifocal lens—with all its innate advantages—is available in Photogray.

AMERICAN OPTICAL
CORPORATION
Optical Products Division • Southbridge, Mass. 01550

# are your contact lens patients afraid of you, doctor?



How about those who lose a lens and never report it to you? Or those who go back to eyeglasses without consulting you? Maybe they simply quit wearing contacts; or maybe they'll go to another specialist for a replacement after a loss.

Either way you both lose. They lose time, money and the benefits that contacts could have given them. You lose a contact lens patient—maybe even the entire patient. The inconvenience and expense of replacing lost lenses are two things your patients don't have to put up with.

RLI can prevent these unknowns from happening to either one of you. We'll be happy to supply you with complete details. Your patients need never be afraid of returning to you for a replacement lens again. Let us prove it! Contact RLI today.

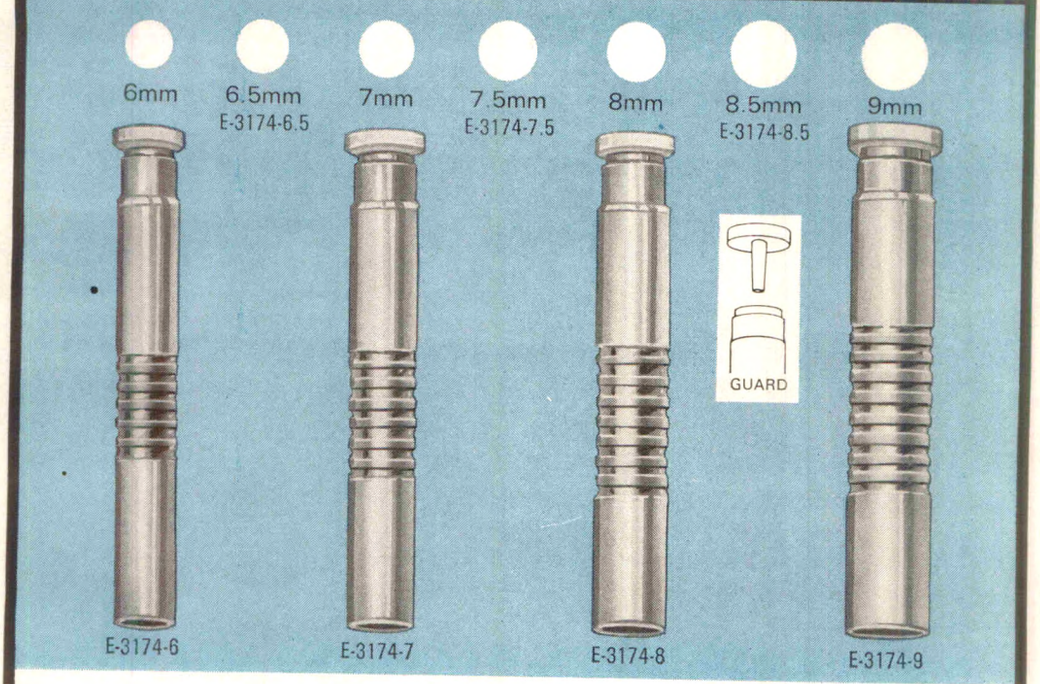
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- All Stainless steel.
- Seven sizes: 6, 6.5, 7, 7.5, 8, 8.5 and 9mm.

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**A NEW PRODUCT:** Implants—Sleeves (Tubes) for preventing adhesions in Eye Muscle Surgery. Method development by Edward A. Dunlap, M.D. Reference: Dunlap, Edward A.: Plastic Implants in Muscle Surgery, Archives of Ophthalmology, 80: 249-257, August 1968.

**TUBING.** *Fully inert because it is made of the same material as the suture;
* Thinnest walls of any surgical tubing, fully transparent and can be *repeatedly* autoclaved;
* Most economical. It is in your interest to compare prices and quality.

**FOIL.** Excellent results with our suture created the demand for Foil for plastic and reconstructive surgery in such cases as orbital fractures, lid reconstruction, etc. Foil is chemically identical with the sutures, thus just as inert when buried in the tissue.

Available in thickness from 0.05mm to 2.00mm, in sheets 15 x 20cm.

Can be steam-autoclaved, cut to size, and carved to shapes and forms.

References: Merrill J. Reeh and James K. Tsujimura: Early Detection and Treatment of Blow-out Fractures of the Orbit, Am. Journal of Ophthalmology, 62: 79-82, 1966. Callahan, Alston: Reconstructive Surgery of the Eyelids and Ocular Adnexa. Aesculapius Publishing Co., Birmingham, Alabama, 1966. Gibis, Paul: Lid Reconstruction and Lifting with Fenestrated Supramid Supports. Klin. Monatsb. Augenh., 112, 3, 1947. J. Barraquer—Z. Cuellar-Montoya: Keratoplasty: Superficial and Deep Corneal Sutures, Annal of Ophthalmology, 1:34-38, 1969. Mustarde, John C.; Jones, Lester T. and Callahan, Alston: Ophthalmic Plastic Surgery Up-To-Date. Aesculapius Publishing Co., Birmingham, Alabama, 1970.

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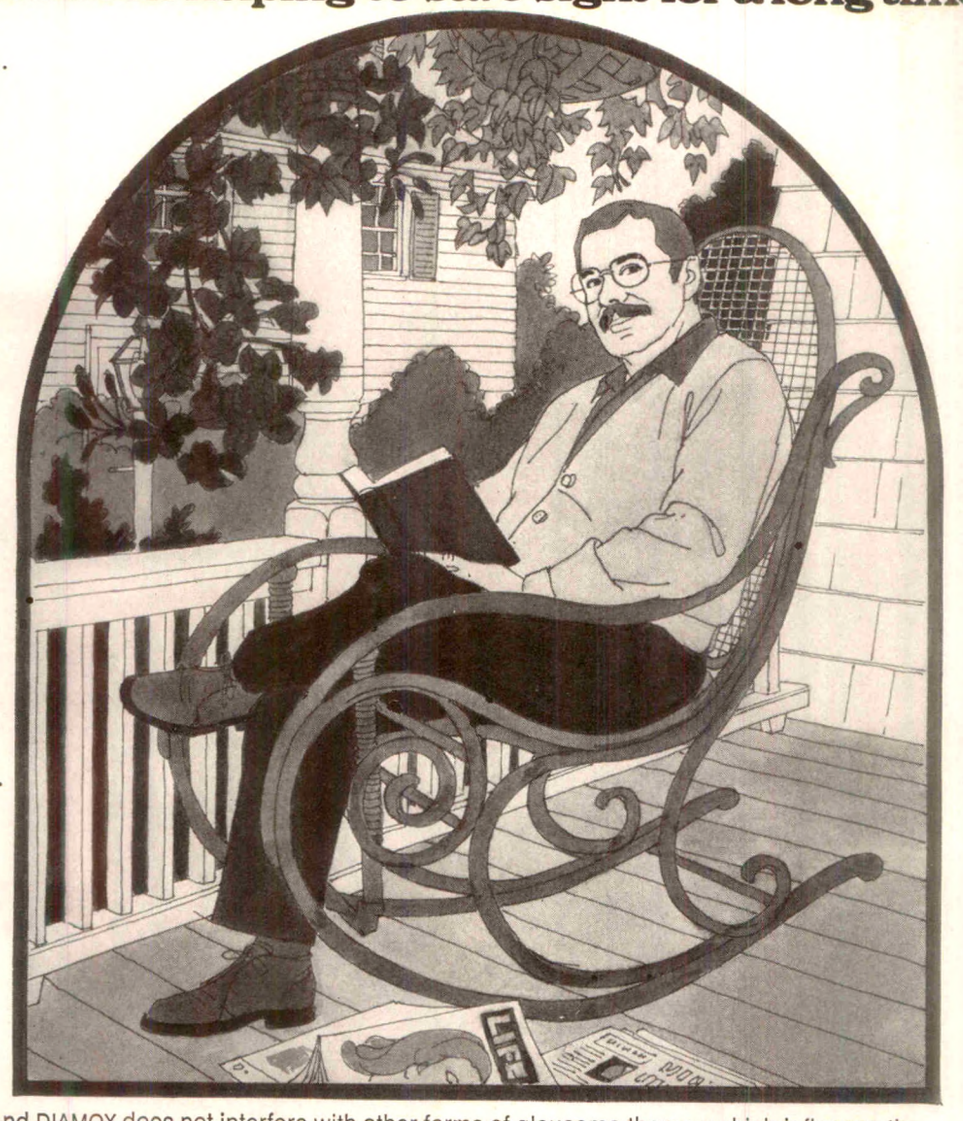
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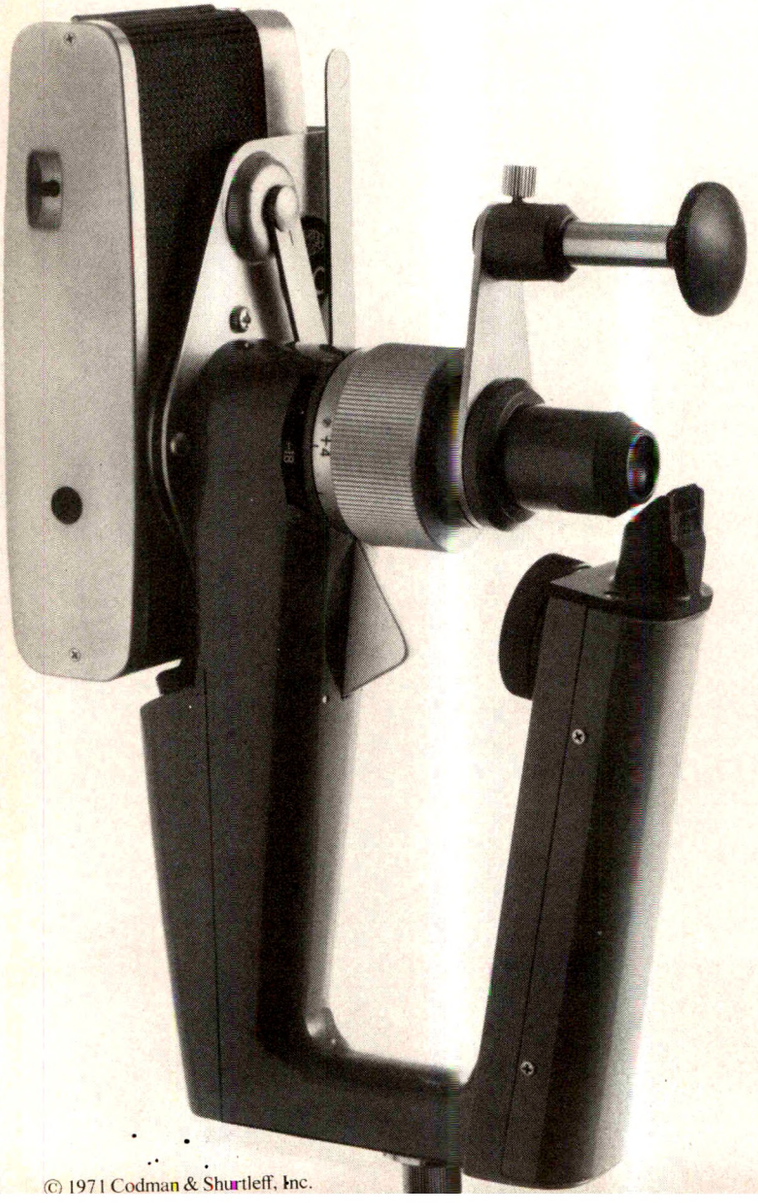
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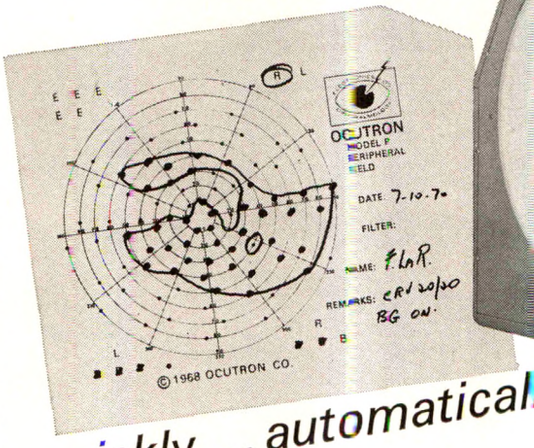

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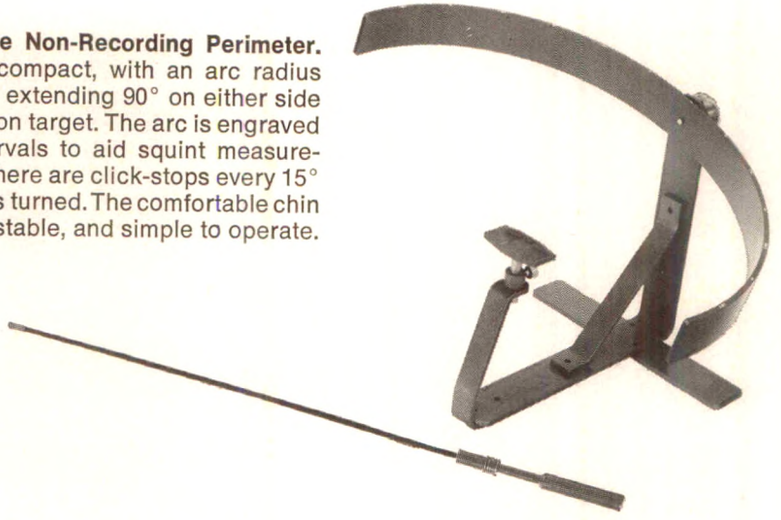
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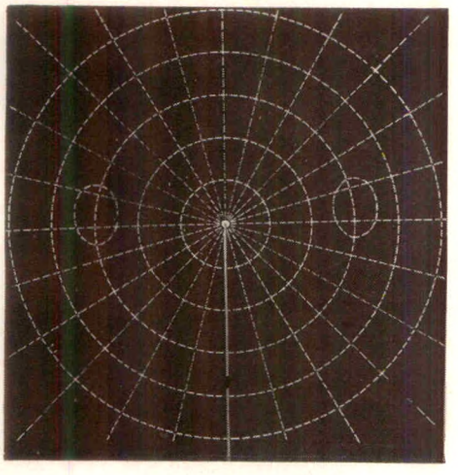
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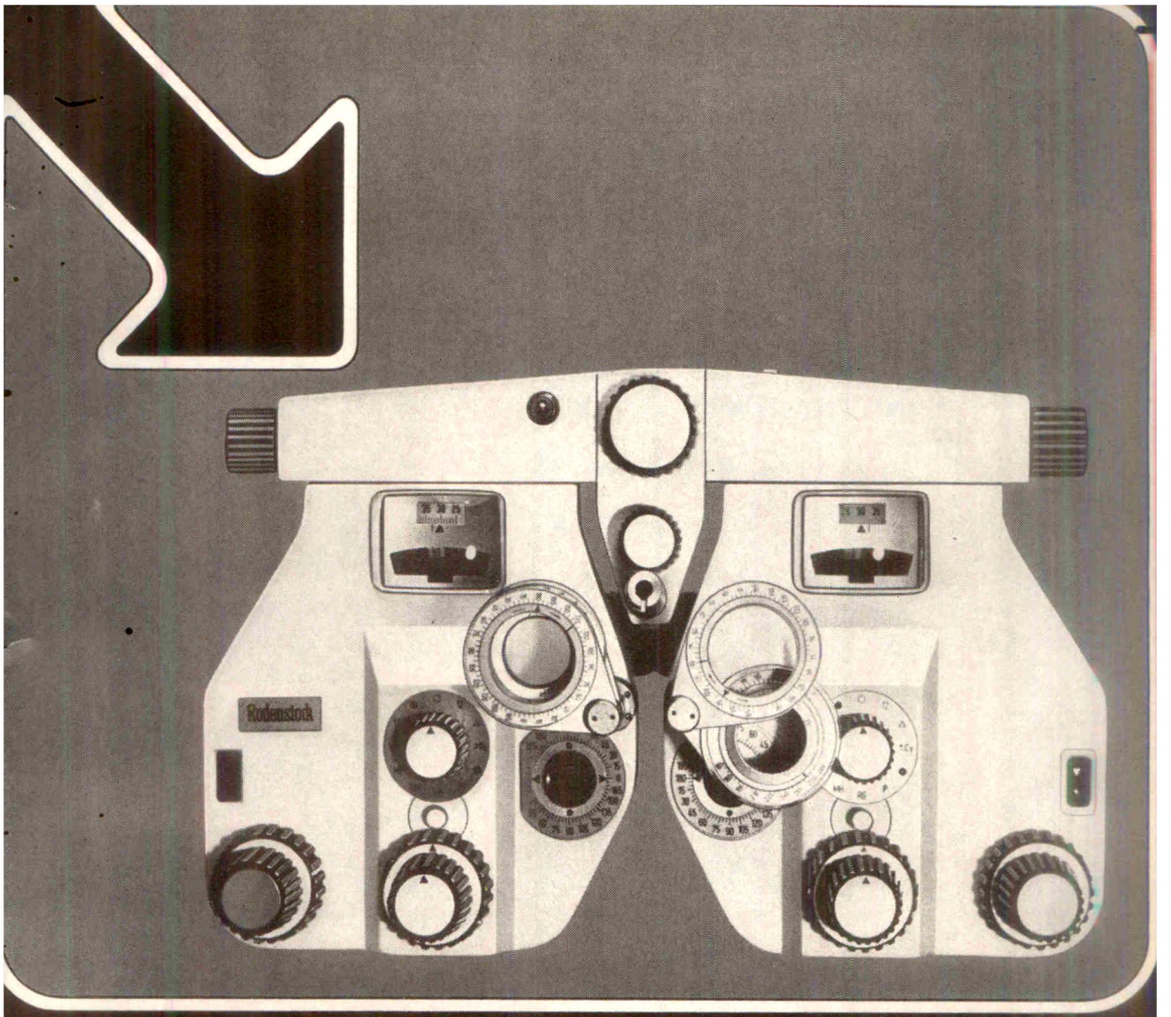
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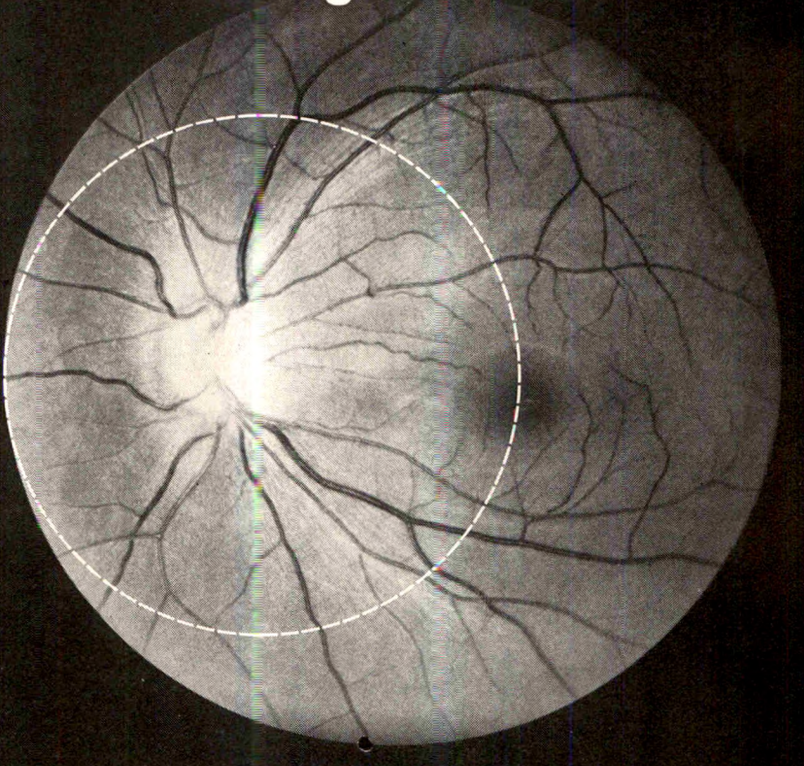
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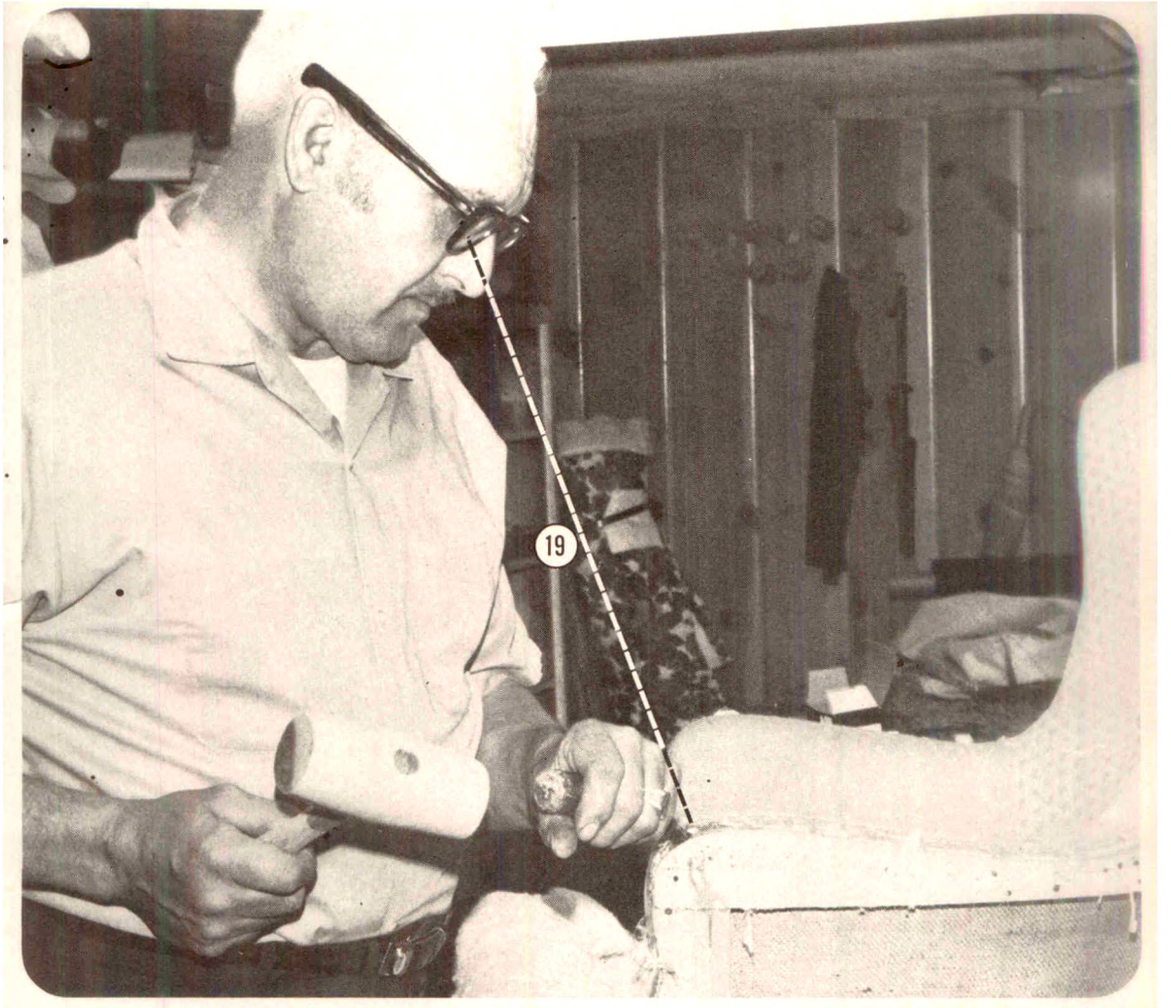
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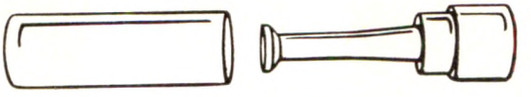
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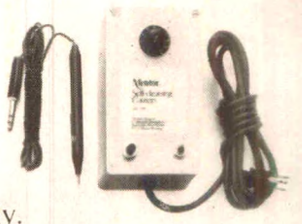
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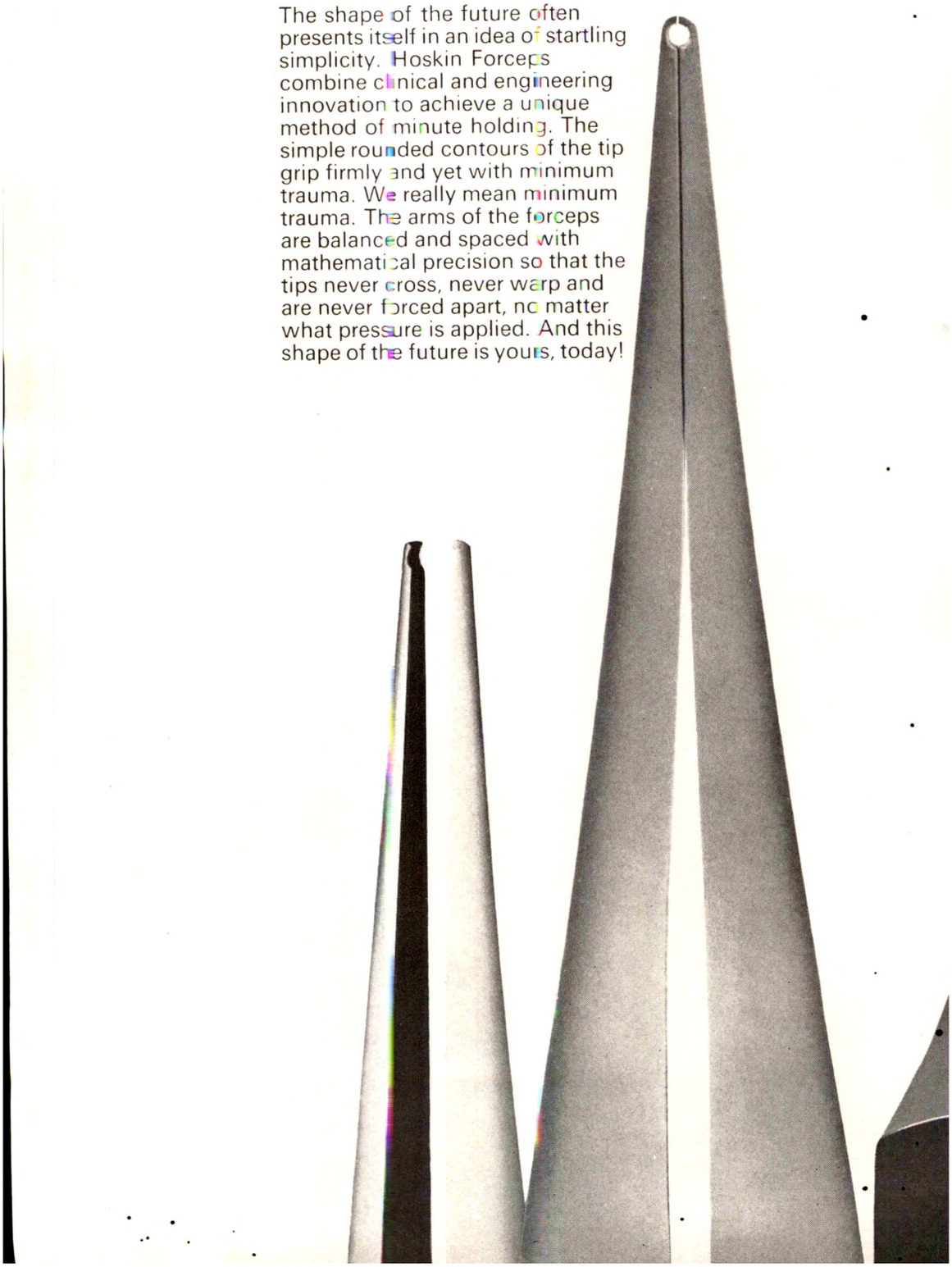
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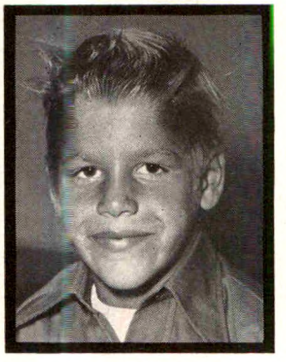

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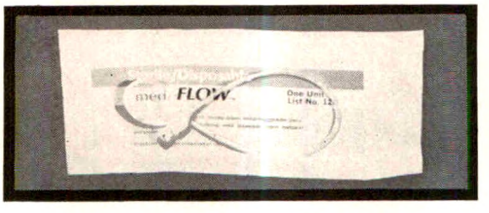
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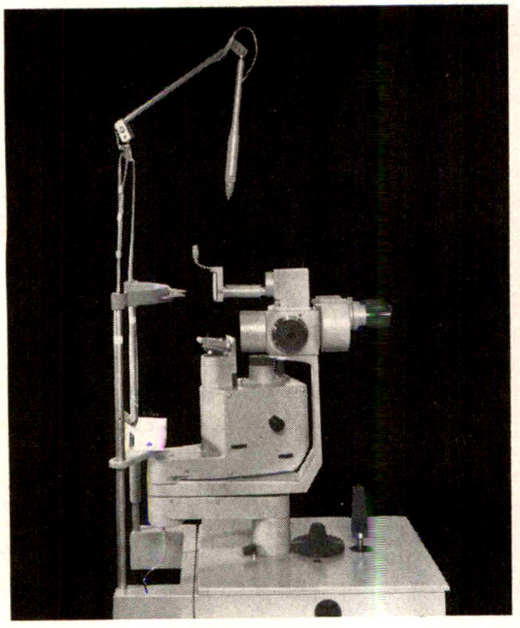
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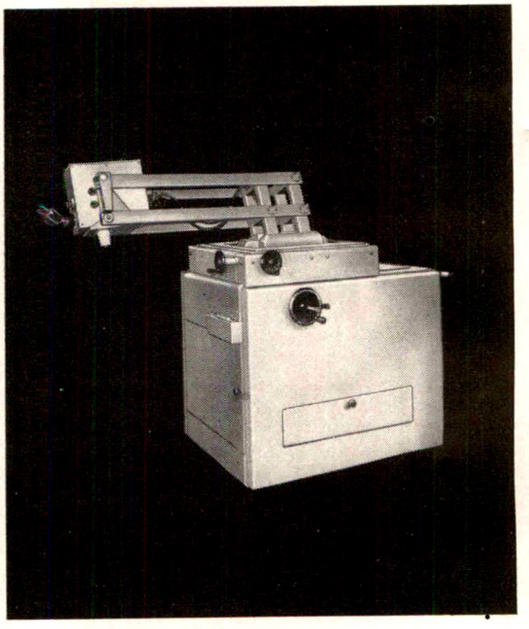
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*Suggestions to Authors* — CONT.

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The manuscript should be arranged in the following order:

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2. Text
3. Acknowledgments
4. References
5. Tables
6. Legends for figures
7. Footnotes

Each major section should begin on a separate sheet.

TITLE PAGE The title page should be numbered Page 1 and contain the title, the authors' names and the address of the author to whom correspondence should be directed. Each subsequent page should include the page number, the senior author's name and an abbreviated (running) title in the upper right-hand corner.

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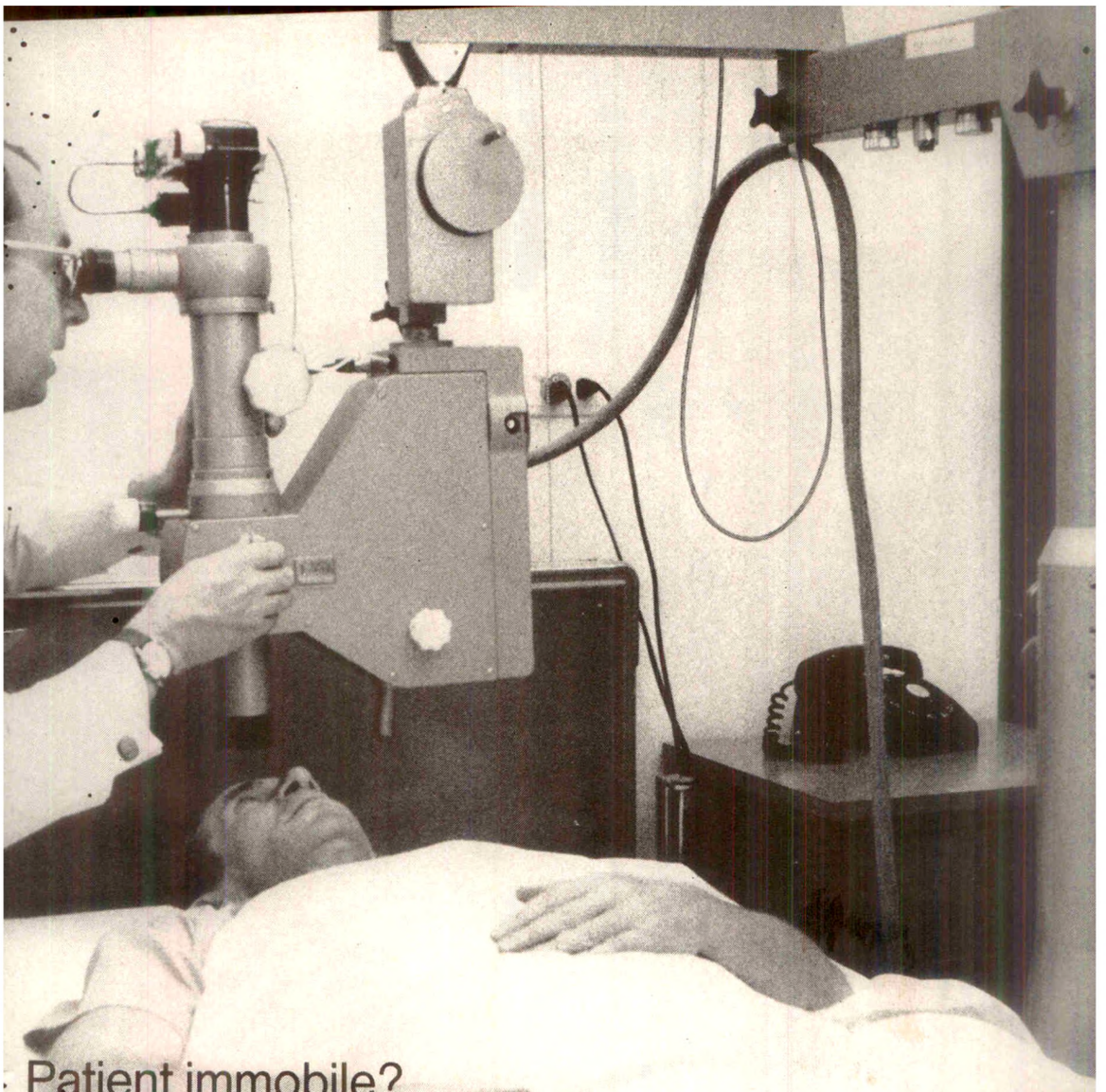
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1. Committee on Form and Style of the Conference of Biological Editors: Style Manual for Biological Journals. Washington, D.C., American Institute of Biological Sciences, 1960.

2. Fishbein, M.: Medical Writing. New York, Blakiston Division, McGraw-Hill Book Company, Inc., 1957.

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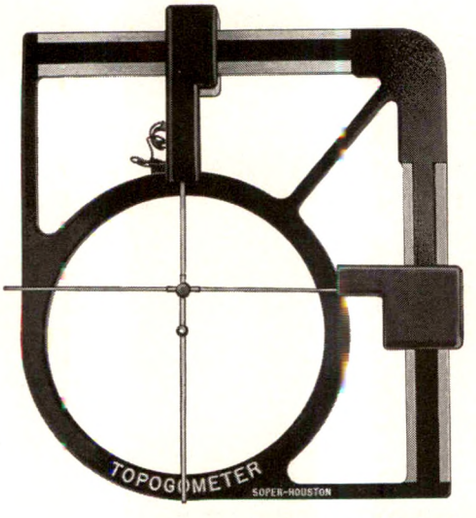
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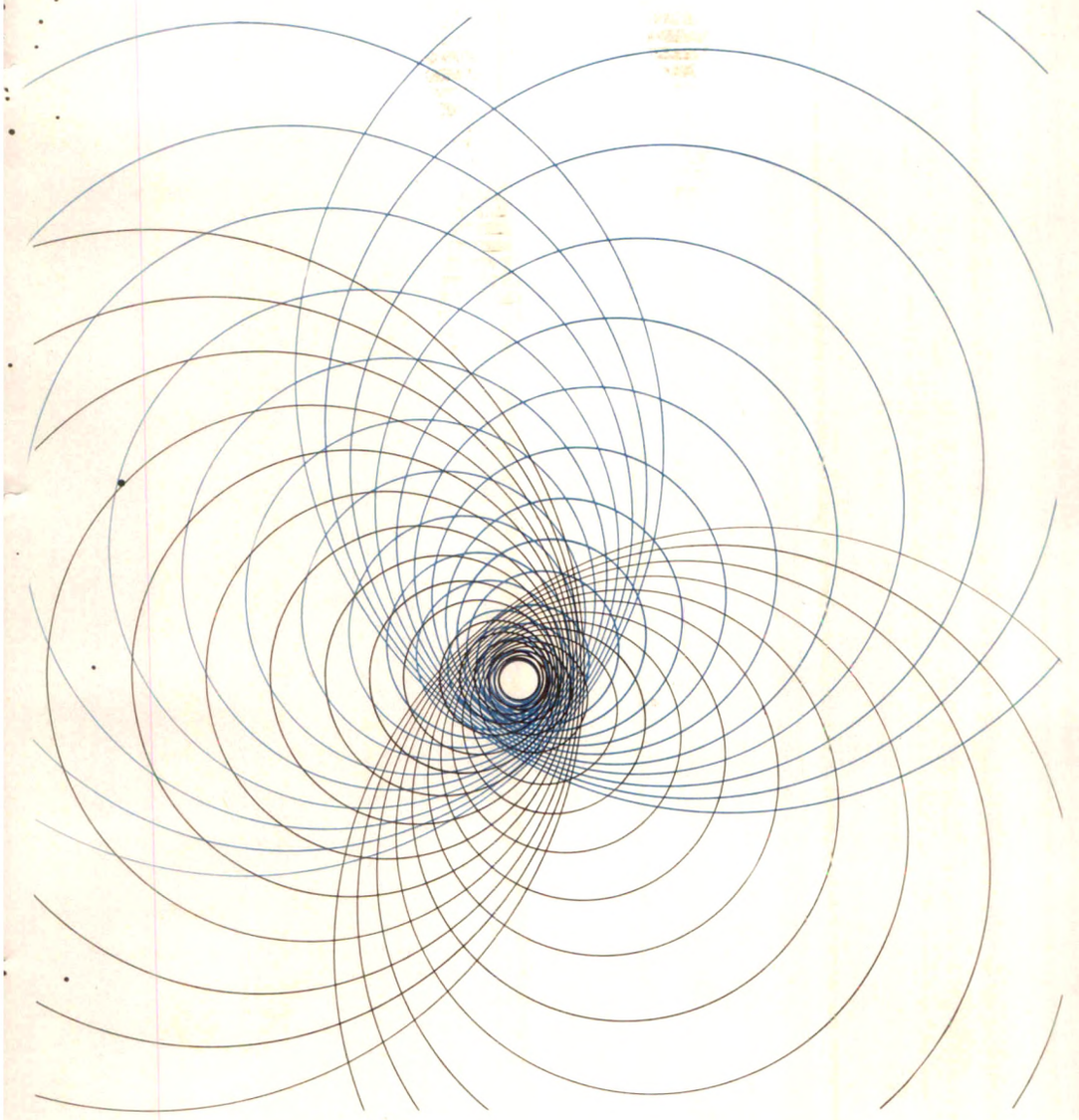
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# The American Society of Contemporary Ophthalmology



## ANNUAL MEETING

**DIPLOMAT**
**HOTEL**
**HOLLYWOOD, FLORIDA**
**February 27-March 3, 1972**

### MONDAY 9:00 A.M.
February 28

**KEYNOTE ADDRESS**
Michael DeBakey, M.D.

Introductory Comments
Morris Fishbein, M.D.

Testimonial to
Guest of Honor
ELMER HOLMES BOBST

Jules Francois, M.D.
Chairman
Yi-Yung Hsia, M.D.
Lawrence Harris, M.D.
Sidney Fox, M.D.
Crowell Beard, M.D.
Byron Smith, M.D.
Pierre Guibor, M.D.

### TUESDAY 9:00 A.M.
February 29

**CATARACT SYMPOSIUM**
Harold Scheie, M.D.
Chairman
Robert Schimek, M.D.
Norman Jaffe, M.D.
Miles Galin, M.D.
Ralph Kirsch, M.D.
John Bellows, M.D.

### 2:00 P.M. to 5:00 P.M.

**GLAUCOMA AND SQUINT**
Saul Sugar, M.D.
Chairman
Miles Galin, M.D.
Milton Best, M.D.
Lawrence Harris, M.D.
Fritz Hollwich, M.D.
Claes Dohlman, M.D.
Edward Dunlap, M.D.

### WEDNESDAY 9:00 A.M.
March 1

**RETINA**
Charles Schepens, M.D.
Chairman
Graham Dobbie, M.D.
Michael Shea, M.D.
Harvey Lincoff, M.D.
Kenneth Hovland, M.D.
C. Hillsdorf, M.D.
Ruth Long, M.D.
H. Freeman, M.D.

**A.M.A. APPROVED**
**CONTINUING EDUCATION COURSES**

**PRACTICAL COURSES**
WEDNESDAY
and
THURSDAY

2:00 P.M. to 5:00 P.M.

Jose Barraquer, M.D.
Chairman

Microscopic Surgery
of the Cornea

Charles Schepens, M.D.
Chairman

Binocular
Ophthalmoscopy

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### THURSDAY 9:00 A.M.
March 2

**CORNEAL SYMPOSIUM**
Herbert Kaufman, M.D.
Chairman
David Donaldson, M.D.
Stuart Brown, M.D.
Donald Willard, M.D.
Jose Barraquer, M.D.
Francisco Barraquer, M.D.

### FRIDAY 9:00 A.M.
March 3

**OCULAR INFECTIONS**
James H. Allen, M.D.
Chairman
Henry F. Allen, M.D.
Herbert Kaufman, M.D.
Roderick Macdonald, M.D.
Theodore Schlaegel, M.D.
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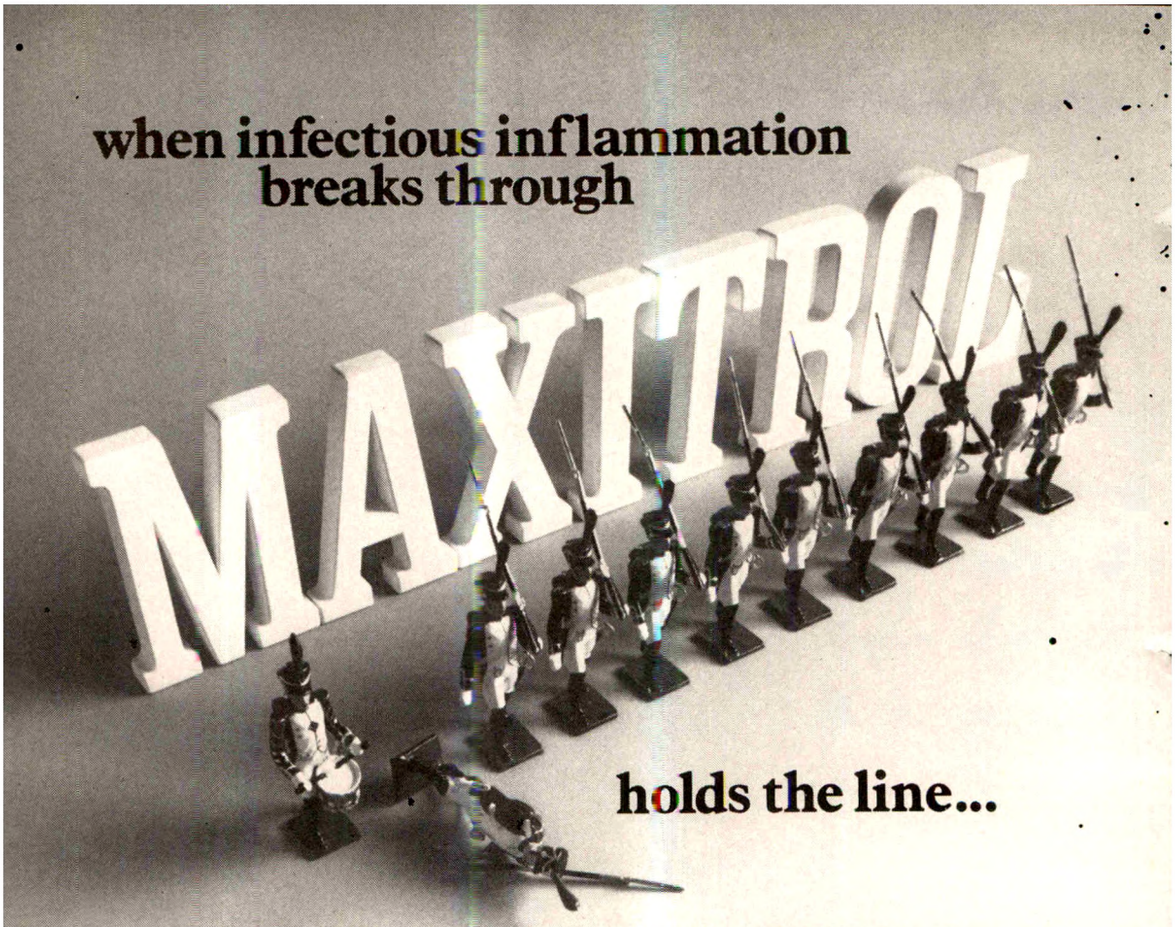
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References: 1. Nelson, E. L.: "Ophthalmic Steroids," in Kaufman, H. E., (ed.): Ocular Anti-Inflammatory Therapy, Chas. C. Thomas, Springfield, Illinois, 1970. 2. Waltman, S. F. and Patrowicz, T. C.: Effects of hydroxypropyl methylcellulose and polyvinyl alcohol on intraocular penetration of topical fluorescein in man. Invest. Ophthal. 9:966, 1970.

AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 72 DECEMBER, 1971 NUMBER 6

# VERHOEFF'S "TERATO-NEUROMA"

## A CRITICAL REAPPRAISAL IN LIGHT OF NEW OBSERVATIONS AND CURRENT CONCEPTS OF EMBRYONIC TUMORS

THE FOURTH FREDERICK H. VERHOEFF LECTURE

LORENZ E. ZIMMERMAN, M.D.

*Washington, D.C.*

It was, of course, a most unanticipated honor for me to be invited to deliver this Fourth Verhoeff Memorial Lecture. Dr. Verhoeff occupied such a remarkable position, not only in the history of American ophthalmology, but especially in the development of ophthalmic pathology in the United States, that I—as a pathologist—am most happy to be able to pay this tribute to him. When he began his work in ophthalmic pathology at the turn of the century, great contributions had been made by the European masters, but on this side of the Atlantic there was only a great void. Once Verhoeff rolled up his sleeves and began his work at the Massachusetts Charitable Eye and Ear Infirmary in Boston, that void soon began to disappear. Before long the Europeans knew they were in for some stiff competition. No one, of course, could have anticipated then that this remarkably energetic man would continue his productive career for another 60-plus years!

I am so very pleased that Dr. Verhoeff did remain active as long as he did, for otherwise I would not have been able to see him in action. When I attended my first meeting of the Ophthalmic Pathology Club in 1954, Dr. Verhoeff was already 80 years old, but who would have thought so once the meeting was under way! No matter what was being presented, Dr. Verhoeff would see things in the contributor's slides that had been overlooked, or he would recall a similar case that everyone else had forgotten, or he would ask a question that no one else had considered.

Dr. Verhoeff had a very bad reputation for being a sort of "people-eater," but, fortunately, he was very kind to me. I guess I was lucky that I didn't enter the field of ocular pathology a decade or two earlier, for I've been told that Dr. Verhoeff did mellow a bit after he became an octogenarian.

Everyone has his favorite stories about Dr. Verhoeff, and Dr. Cogan even coined a new term to officially recognize them when he delivered the Third Verhoeff Lecture,[1] so let me add my contribution to this "Verhoeffiana."

I am sure that many of you will recall that the Ophthalmic Pathology Club used to meet in Washington just before the Wilmer meeting in Baltimore and that Dr. Verhoeff was always a prominent figure in the front row

From the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology, Washington, D.C. Supported in part by Public Health Service Training Grant EY-00032 from the National Eye Institute.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Presented at the 107th annual meeting of the American Ophthalmological Society, Hot Springs, Virginia, May 25, 1971.

Reprint requests to Lorenz E. Zimmerman, M.D., Chief, Ophthalmic Pathology Branch, Armed Forces Institute of Pathology, Washington, D.C. 20305.

at the Wilmer meeting, where he was usually called on to initiate the discussion of almost every paper. The episode I will recount took place at the 1956 Wilmer meeting, when Professor Alan Woods was still Chairman of the Department of Ophthalmology at Johns Hopkins. This was just a few years after Hellie Wilder had published her epochal paper[2] establishing toxoplasmosis as an important cause of chorioretinitis in adults and just two years after T. gondii was first recovered from the eye of an adult patient at the Walter Reed Army Hospital.[3] Professor Woods had selected for his traditional opening lecture of the annual Wilmer meeting a review of the toxoplasmosis story in relation to his clinical and laboratory investigations of uveitis patients studied at the Wilmer Institute.[4] Dr. Verhoeff opened the discussion by immediately shocking the audience with his statement that Professor Woods and everyone else interested in ocular toxoplasmosis had overlooked the fact that he himself had more than 25 years earlier presented an excellent, detailed description of the clinical and pathologic features of Toxoplasma chorioretinitis. I still vividly recall how stunned I was by such an impossible claim. I feared that Dr. Verhoeff's age was getting the best of him, but then—just as a ripple of skeptical snickering was beginning to go through his audience—Verhoeff explained, "the only trouble is that I called it tuberculosis."[5]

That experience taught me several things about Dr. Verhoeff. At the age of 82 he was still very "sharp" and had a great sense of humor. He was honest. In his original description of the case that he diagnosed as one of localized tuberculous chorioretinitis,[5] he had admitted that he could not demonstrate any acid-fast bacilli. Instead of leaving this mistake buried, he was bringing it out in the open. He recalled his case vividly enough to be able to make the correct diagnosis in retrospect, and I believe his revised diagnosis of toxoplasmosis was the correct one because his published photographs certainly are most consistent with such an interpretation.

Two-thirds of a century ago, at the 40th annual meeting of the American Ophthalmological Society in Atlantic City, Verhoeff—then a guest of the Society—described in minute detail a rare tumor that arose from the pars ciliaris retinae.[6] Although he considered it a "terato-neuroma," his description is now generally accepted as the classic reference for the intraocular medullo-epithelioma (or "diktyoma," as many still prefer to call this tumor). While justly proud of his original contribution and of the wide recognition it subsequently received, not only in ophthalmologic circles but also by such an eminent oncologist as Willis,[7] and by such authoritative neuropathologists as Russell and Rubinstein,[8] he was nevertheless miffed by the fact that his name for the tumor never became very popular. In discussing a paper entitled "Intraocular diktyoma and glioneuroma," by Fralick and Wilder[9] at the 1949 meeting of this Society, Verhoeff typically and inimitably made the following remarks:

> In their very interesting paper the essayists indicate that I was the first to point out the real nature of the type of tumor with which they are dealing. I did this in a paper read by invitation before this Society 45 years ago, and I therefore cannot deny the allegation. Scarcely a member is now alive who remembers that famous day and year. I recall that I exceeded the time limit and the Society voted me an indefinite extension of time. I hope this carries over to include my present discussion.
>
> The case I reported was all mine, clinically and pathologically. Conditions were different in those days. I removed the eye, embedded it, repaired the microtome, sharpened the microtome knife, cut all the sections, prepared all the staining fluids, stained the sections by various methods, modified Mallory's method for neuroglia, made the drawings, supervised the making of the photomicrographs, made the lantern slides, and typed the manuscript on a Blickensdörfer typewriter. I did not sweep out the laboratory—a cross-eyed orderly did this.
>
> Fuchs never had one of these cases, but studied sections of such tumors reported before 1908 by other observers. I sent him a full set of sections of my tumor, including some stained differentially. In his paper he accepted all my views as to the nature of these tumors—in fact, he made them his own. But he rejected the name I suggested—terato-neuroma, meaning a monsterlike growth consisting primarily of nervous tissue—and brought forward the name "diktyoma." This term, five years previously, had been devised by Emanuel for the tumor now

called retinoblastoma. In my opinion it is not a good name for either tumor. That its meaning lacks precision is shown by the fact that it has been used for two such different tumors. My tumor contained embryonic retina, abnormal neuroglia, and embryonic vitreous. It showed what appeared to be abortive attempts to form whole embryonic eyes. The tumor of the essayists contains embryonic retina, neuroglia, fibrous tissue, and cartilage. Formation of embryonic vitreous if it occurs is not conspicuous. The tumor is said to contain ganglion cells, but it is not stated how these were identified. There is no evident reason why such a tumor should not contain ganglion cells, but atypical glial cells can closely resemble ganglion cells. I should like to ask whether or not Nissl bodies were demonstrated. Obviously the term "diktyoma" is inadequate for these tumors. The essayists realized that this was so in their case, for they found it necessary to add the term "glioneuroma." If they had used my term, terato-neuroma, this addition would have been needless.

Verhoeff then concluded his discussion of the Fralick-Wilder paper by showing some of his original slides and in doing so stated, "It might be well to show these every 45 years." How I wish that he were here today so that he could give a spicy rebuttal to some of the criticisms I shall be making of his pet name, for while I agree with him that terato-neuroma would have been an entirely appropriate designation for the tumor described and illustrated by Fralick and Wilder, I don't agree that it was a suitable name for his original medullo-epithelioma.

For this Verhoeff Lecture, then, I have chosen to review Verhoeff's original description of his tumor and his concept of the nature of that tumor, which led him to propose the name "terato-neuroma." I shall do this in the light of my own experience, based on a recent re-examination of over 100 tumors of the ciliary epithelium on file in the Registry of Ophthalmic Pathology.[10] These rare tumors exhibit many histologic variations from case to case, and it is therefore easy for the pathologist who hasn't had the benefit of a large experience to become so impressed by certain features of a given case that he misses the "big picture." Fortunately, however, Verhoeff, in his original description, did describe and emphasize the most significant features that distinguish this tumor from others with which it might be confused. It is a tribute to his powers of observation and his facility for detailed description that his paper has become a classic. Independently, when I first became interested in these tumors several years ago, I made a number of the same observations and arrived at some of the same interpretations[11] as Verhoeff had done many years earlier, and for a long while I believed them to be "original," as I had not then read Verhoeff's ancient paper. What a surprise when subsequently I found out that Verhoeff had "scooped" me by more than half a century!

Verhoeff's patient was a two-and-one-half-year-old child whose affected eye had become blind, cataractous, and enlarged from secondary glaucoma by the time the parents brought her in for enucleation. Retinoblastoma ("glioma retinae") was the preoperative diagnosis. Upon opening the eye, Verhoeff found a tumor that arose from the ciliary body in the upper nasal quadrant, filled the posterior chamber in that area, and displaced the cataractous lens, pushing it aside. It had many excrescences over its surface, and there were, in addition, many tiny globular bodies attached to the pupillary margin of the iris. Microscopically,* Verhoeff found the tumor to have had its origin in nonpigmented ciliary epithelium (pars ciliaris retinae) of the pars plicata (Fig. 1). It produced intricate convolutions enclosing lumina of various shapes and sizes. The structures forming these convolutions were chiefly of two types. One, which Verhoeff considered the more primitive form, consisted of a single layer of columnar epithelium with oval vesicular nuclei and staining more deeply than the normal ciliary epithelium. The other consisted of thicker bands composed of multilayered elongated cells. One border of these bands was typically sharply defined and resembled the outer lim-

*I had hoped to be able to show photomicrographs from Verhoeff's original case but was unable to obtain any photogenic slides, so I will substitute photomicrographs from other cases in the Registry.

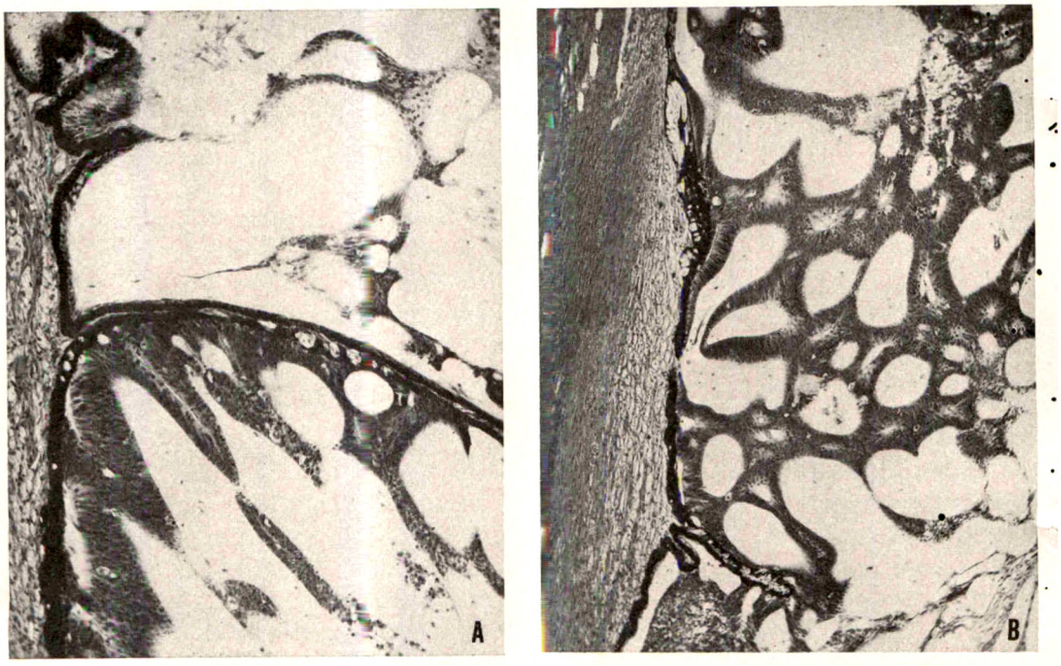



Fig. 1 (Zimmerman). The medullo-epithelioma arises from the nonpigmented ciliary epithelium and produces intricate convolutions enclosing lumina of various shapes and sizes. The neoplasm is composed of structures resembling the medullary epithelium of the embryonic ciliary epithelium and retina (hematoxylin and eosin, left: ×115, right: ×80). (AFIP Negs. 70-9497-9).

iting membrane of the embryonic retina (Fig. 2). Mitotic figures were generally most conspicuous along this surface of the bands. The opposite surface was less well defined but was almost always intimately united with a "fibrillated connective tissue not to be distinguished from viteous humor." Verhoeff stressed that "this vitreous humor has not simply been enclosed by the tumor, since the latter does not come in contact with

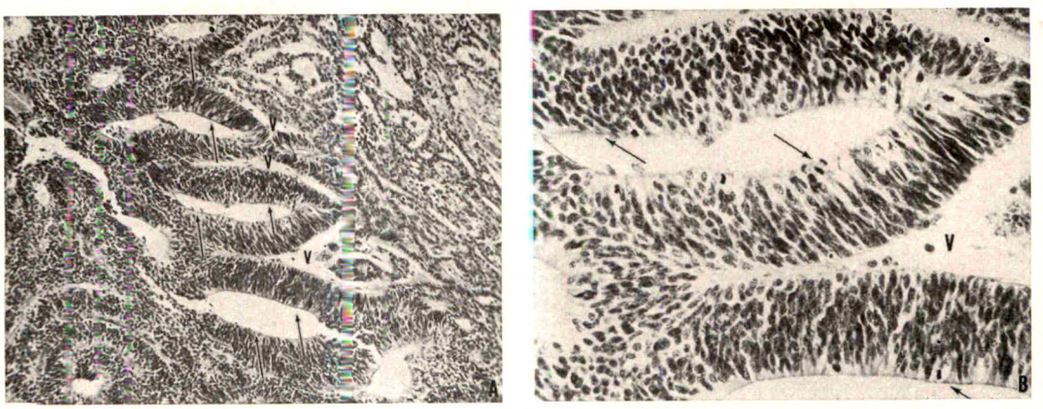



Fig. 2 (Zimmerman). (A) The multicellular bands are polarized, forming a sharply defined structure analogous to the external limiting membrane of the retina along one surface (arrows); the less well-defined opposite surface is in contact with primitive vitreous (V) (hematoxylin and eosin, ×115). (AFIP Neg. 70-8363). (B) The center of the field shown at left has been enlarged, revealing considerable mitotic activity along the outer limiting membrane but hardly any along the vitreal surface (hematoxylin and eosin, ×305). (AFIP Neg. 70-8362).

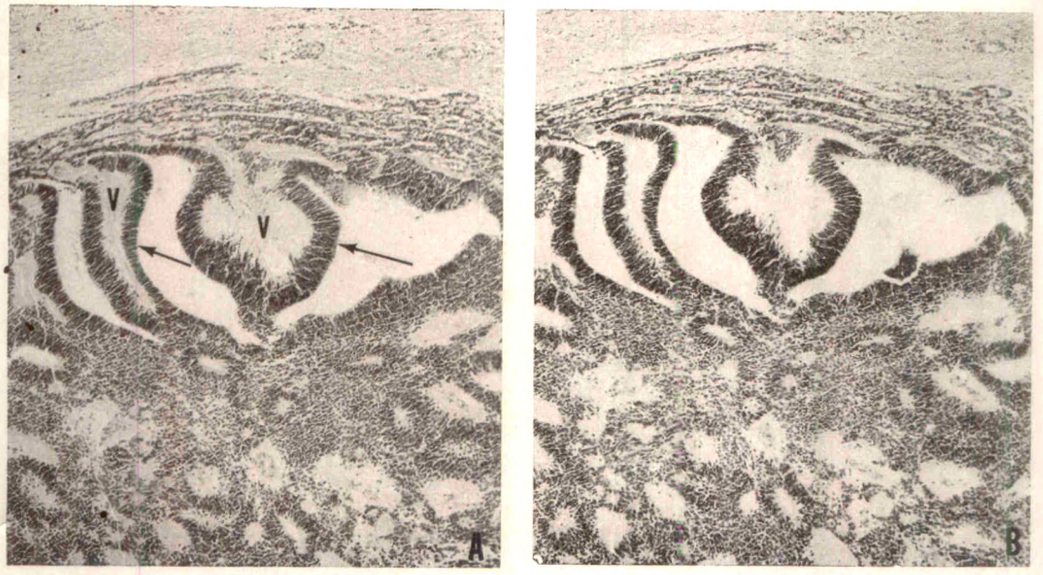



Fig. 3 (Zimmerman). (A) In contrast with the structures shown in Figure 2, in which the luminal surfaces of the bands are formed by the external limiting membrane and the lumina are empty, here the concavities are filled with vitreous (V) and the outer convex surfaces (arrows) are formed by the external limiting membrane. The vitreous is easier to visualize here than in Figure 2 because the section was stained by alcian blue (×60). (AFIP Neg. 70-8365). (B) Adjacent section to that used for A, but before staining with alcian blue the section was treated with hyaluronidase. The vitreous is now unstained by alcian blue (×60). (AFIP Neg. 70-8366).

the normal vitreous humor, but it is newly formed, and the stages in its formation can be easily traced." Verhoeff pointed out that, depending upon how these bands were folded, one could see various patterns. Sometimes one could see lumina that were generally empty or perhaps filled only with cell debris or serum, bounded by the external limiting membrane (Fig. 2). In such instances, the bands circumscribing such structures were surrounded by the delicate connective tissue resembling embryonic vitreous. In other instances, the globoid bodies contained the embryonic vitreous and the outer surface of the bands was outlined by the external limiting membrane (Fig. 3).

In my own studies of this curious structure of these tumors, I had the advantage of some newer stains that were not available in Verhoeff's day—stains that vividly reveal the acid mucopolysaccharide in the vitreous.[12] These stains provided dramatic confirmation of Verhoeff's observations (Figs. 3 and 4). The cellular bands that produce the characteristic diktyomatous pattern of these medullo-epitheliomas, whether they be those that resemble the embryonic ciliary epithelium or those that resemble embryonic retina, are strikingly polarized, forming a fenestrated membrane corresponding to the external limiting membrane along one surface while producing embryonic vitreous along the other.[11]

So much for our basic points of agreement about the structure of these tumors. Wherein do we disagree? Verhoeff shared the classic views of the day concerning formation of the vitreous humor. This was regarded as a product of the mesoderm. He believed that blood vessels and associated mesodermal structures derived from the stroma of the ciliary body were carried into the lesion and were responsible for the formation of the vitreous humor that appeared to be such an integral part of the tumor. Verhoeff envisaged the neoplasm as making "abortive attempts to form eyes," and since he regarded the formation of vitreous as a

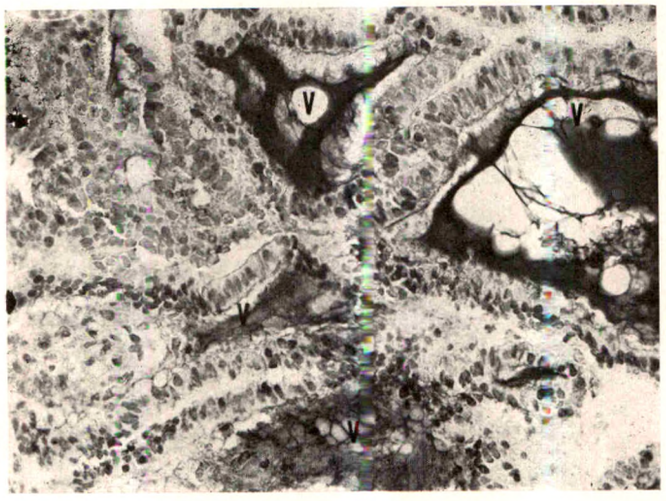



Fig. 4 (Zimmerman). In this preparation the embryonic vitreous (V) is deeply stained by alcian blue. Observe that this vitreous is never present along both surfaces of the medullary epithelium, just as the embryonic vitreous is never formed along both surfaces of the embryonic retina and ciliary epithelium (×305). (AFIP Neg. 63-2182).

function of the mesoderm, he thought the tumor was more closely allied to the teratomata than to any other recognized class of tumors. Moreover, he felt the complexity of its structure, the degree of its differentiation, and the early period of life at which it occurs were all consistent with this suggestion.

Already at the time of his paper, Verhoeff was aware of the fact that some investigators were challenging the traditional concept of the vitreous as a product of the mesoderm. He cited the "recent views of Haemers and others, who believe it to be derived from the neuroglia of the retina," but he rejected this suggestion because his own observations, making use of a variety of special staining methods, led him to the conclusion that the fibrils in the vitreous did not take origin from the retina. Since then, however, embryologists and others have largely come to agreement that the medullary epithelium does play a most important rôle in the formation of the embryonic vitreous.[11,13-15]

That the mucoid material resembling primitive vitreous contained within some of the vesicles cannot be ascribed to mesodermal elements carried into the tumor from the stroma of the ciliary body is established by those cases in which free-floating vesicles in the anterior chamber have been observed over a period of time during which they progressively enlarged.[16,17] In such cases there may be no connection of these vesicles to the iris or ciliary body (Fig. 5). As Treacher Collins pointed out in his discussion of the remarkable case reported by Spicer and Greeves,[16] it demonstrated how pathology can help to explain embryologic processes. He stated, "It used to be generally thought that the vitreous humour was of mesoblastic origin; but of late embryologists had regarded it as derived from the neural epiblast; and this specimen bore out that view very conclusively. Further, it showed not only that the vitreous humour was derived from the secondary optic vesicle, but that it came from only the front part."

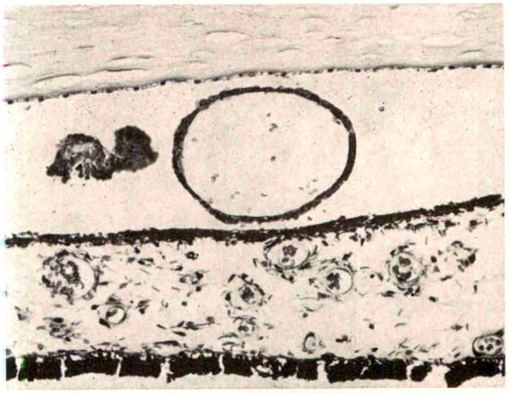


Fig. 5 (Zimmerman). Free-floating "cyst" in anterior chamber. Material indistinguishable from vitreous fills the lumen (alcian blue, ×140). (AFIP Neg. 71-5601).

Thus, a major blow to Verhoeff's concept is the fact that he did not demonstrate convincingly that his tumor had intrinsic elements representative of germ layers other than the neural ectoderm. Interestingly, however, earlier at the same meeting in 1904, Alling[18] had presented the case of a four-year-old child whose enucleated eye had been found to contain a congenital tumor of the ciliary body containing cartilage as well as epithelium. The tumor had been studied microscopically by Arnold Knapp, who considered it an undifferentiated (embryonal) tumor. From the description and from the remarkably good photomicrographs that document the case report, I am convinced that Alling's case was indeed a medullo-epithelioma of the ciliary body containing cartilage. Verhoeff's had been sent sections of that tumor, and he commented on the case after it was presented at the meeting. Strangely, Verhoeff did not recognize it as related to his own tumor, and, in fact, stated that he believed it was an endothelioma! Had he recognized Alling's tumor for what it was—a teratoid medullo-epithelioma—he would have been able to make a much better case for his name, "terato-neuroma."

There is, however, still another objection to that name, "terato-neuroma." As Willis[19] points out, ever since Virchow's time the term "neuroma" has been reserved for tumors that contain mature neurons. Verhoeff made no claim that his tumor contained such elements; to the contrary, it consisted of immature derivatives of the primitive medullary epithelium. It is difficult to understand, therefore, why the term "medullo-epithelioma" did not appeal to Verhoeff.

Verhoeff stated that he knew of no class of tumors other than the teratomata with which his tumor might be more appropriately grouped. There is, however, a group that Willis[20] calls the "embryonic tumors," which he defines as tumors that arise during embryonic, fetal, or early postnatal development from a particular organ, rudiment, or tissue while it is still immature. He also points out that some embryonic tumors also show divergent differentiation (heteroplasia), forming tissues of kinds that do not normally occur in the part. A familiar example would be the presence of rhabdomyoblasts in an embryonic tumor of the kidney (Wilms' tumor). I agree fully with Willis that the medullo-epitheliomas of the ciliary body logically belong in the group of embryonic tumors.

The cases presented to this Society by Alling and by Fralick and Wilder contained islands of hyaline cartilage; since then cartilage has frequently been found in the loose mesenchymal tissue associated with these medullo-epitheliomas (Fig. 6).[21] Differentiation into brain tissue has also been observed in a number of them (Fig. 7).

Before leaving the subject of names and classifications of tumors of the ciliary epithelium, I should point out that because I couldn't find a good classification of these tumors, I was forced to develop one of my own.[10] Fuchs[22] made an astute observation that is still generally correct. He noted that they could conveniently be placed in two main groups: (1) those occurring in children and resembling embryonic retina, which he called diktyomas, and (2) those of adults representing neoplastic transformation of hyperplastic epithelium, usually in eyes that had been inflamed or traumatized. Fuchs's name, "diktyoma," was selected to call attention to the network of medullary epithelial bands that are so conspicuously present in some of these tumors of infancy. I have already cited Verhoeff's objections to the name "diktyoma." Russell and Rubinstein[8] summed up the situation very well: "Apart from brevity, this term has little to recommend it." Strangely, it continues to enjoy considerable popularity. I must confess that unless I watch very carefully I find myself using "diktyoma" instead of "medullo-epithelioma"!

Grinker[23] apparently first introduced the term "medullo-epithelioma," but based it, at least in part, on a misconception. He stated,

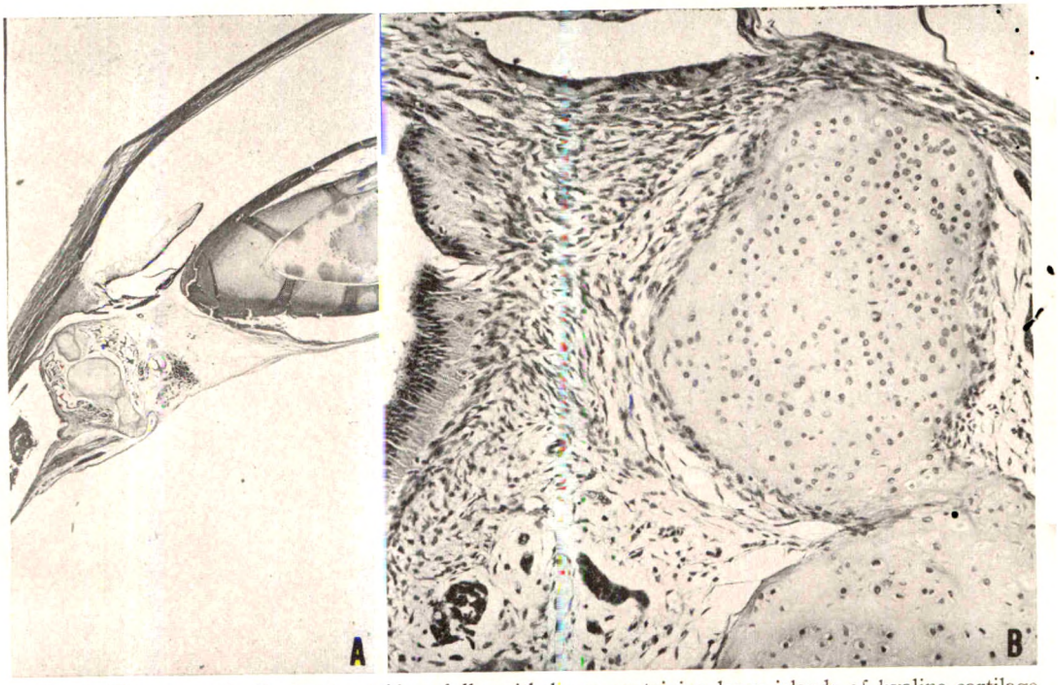



Fig. 6 (Zimmerman). Benign teratoid medullo-epithelioma containing large islands of hyaline cartilage embedded in a loose mesenchymal stroma. (hematoxylin and eosin, left: ×10, right: ×115). (AFIP Negs. 70-8774-5).

"In the retina, medullary epithelium persists in almost undifferentiated form throughout adult life in the epithelium of the pars ciliaris retinae, and it is from this tissue that medullo-epitheliomas of the retina usually arise." Actually, the ciliary epithelium is not poorly differentiated tissue, and the acquired tumors that arise from it do not resemble the medullo-epitheliomas that arise from the embryonic medullary epithelium. Nevertheless, certain authoritative writers such as Andersen,[21] Duke-Elder and Perkins,[24] and Reese,[25] have followed Grinker's suggestion and have lumped together both embryonic and

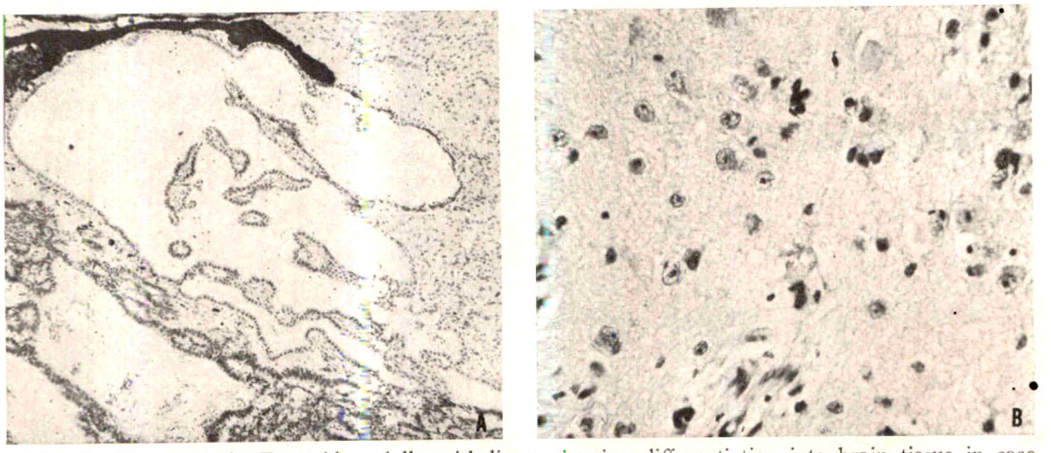



Fig. 7 (Zimmerman). Teratoid medullo-epithelioma showing differentiation into brain tissue in case reported by Fralick and Wilder[9] (hematoxylin and eosin, left: ×80, right: ×305). (AFIP Negs. 70-8774-5).

acquired tumors of the ciliary body under the heading of medullo-epithelioma. In Andersen's classification,[21] the former are called embryonal medullo-epitheliomas, the latter adult medullo-epitheliomas. Both designations are objectionable. To better understand why these are objectionable, let me again make reference to Willis's concept of medullo-epitheliomas. These are considered embryonic tumors, neoplasms that arise from embryonic or fetal tissues. Following this concept, the term "embryonal medullo-epithelioma" becomes redundant (medullo-epitheliomas are by definition embryonic neoplasms) and "adult medullo-epithelioma" becomes contradictory. Duke-Elder and Perkins[24] tried to classify these tumors, but their classification is also objectionable on several grounds. They, too, place "adult epitheliomas" under the heading of medullo-epitheliomas, and all of these are grouped among the malignant neoplasms. They apparently do not recognize a benign form of medullo-epithelioma. While I am criticizing the classification proposed by others, I should also admit that the discussion of these tumors that Hogan and I[26] gave in our book, Ophthalmic Pathology, is very poor and our classification of them is totally inadequate. These deficiencies will be corrected in our next edition!

From a conceptual point of view I believe it is logical (and probably correct) to assume that intraocular medullo-epitheliomas are congenital neoplasms. At least the anlage from which the tumors arise is undoubtedly present at birth even though the clinical manifestations of the tumor that lead to its recognition may not develop until long after birth. In striking contrast, the group that other authors have called "adult medullo-epitheliomas" arise, I believe, from fully differentiated ciliary epithelium that subsequently undergoes neoplastic change, not infrequently after having passed through a stage of non-neoplastic reactive hyperplasia (pseudoadenomatous hyperplasia). Thus, I recently suggested[10] that we divide these epithelial tumors of the ciliary body into two main groups, the congenital and the acquired (Table 1).

Just a word about the glioneuroma: We have only two examples, the one recorded by Kuhlenbeck and Haymaker[27] and a remarkably similar unpublished case presented to the Verhoeff Society by Dr. William Spencer of San Francisco. In both of these cases, a large part of the anterior segment of the eye was replaced by a large mass of very mature, well-differentiated brain tissue containing neurons as well as glia. None of the usual embryonic retina, ciliary epithelium, and primitive vitreous characteristic of medullo-epitheliomas was present. Glioneuromas belong in the class of choristomatous malformations, portions of the iris and ciliary body having failed to develop normally and having produced instead large, well-differentiated masses of tissue resembling brain.[10]

With the exception of these rare glioneuromas, the congenital group comprises the "pure" and the "teratoid" medullo-epitheliomas. The "pure" medullo-epitheliomas by definition contain elements that closely resemble the medullary epithelium, but in addition they may also contain structures resem-

TABLE 1

NEUROEPITHELIAL TUMORS OF THE CILIARY BODY

| |
|---|
| I. Congenital |
| A. Glioneuroma |
| B. Medullo-epithelioma |
| 1. Benign |
| 2. Malignant |
| C. Teratoid medullo-epithelioma |
| 1. Benign |
| 2. Malignant |
| II. Acquired |
| A. Pseudo-adenomatous hyperplasia |
| B. Adenoma |
| 1. Solid |
| 2. Papillary |
| 3. Pleomorphic |
| C. Adenocarcinoma |
| 1. Solid |
| 2. Papillary |
| 3. Pleomorphic |

bling those derived from the secondary optic vesicle or optic cup; of these, the most frequently observed are retinal pigment epithelium, ciliary epithelium, vitreous, and neuroglia. In the malignant varieties one also sees masses of tightly packed neuroblastic cells, sometimes showing marked mitotic activity, making these tumors indistinguishable from poorly differentiated retinoblastomas. Structures resembling poorly differentiated Flexner-Wintersteiner rosettes may also be observed (Fig. 8).

To qualify as a teratoid medullo-epithelioma there must be one or more heteroplastic elements present in addition to the medullo-epitheliomatous components. From Verhoeff's description and illustrations of his tumor, we would have to assume that there were no truly heteroplastic elements present. By far the most frequently observed heteroplastic element in medullo-epitheliomas is hyaline cartilage (Fig. 6); next is tissue resembling brain (Fig. 7). Recently we have become aware of the fact that skeletal muscle may also be present, usually resembling the moderately well-differentiated rhabdomyosarcomas.[10,28]

One of the most interesting teratoid medullo-epitheliomas that I have seen (Fig. 9) contained remarkably organoid formations consisting of a central tubular structure lined by medullary epithelium oriented as in the primary optic vesicle with a sharply outlined inner limiting membrane along the luminal surface and much less sharply outlined surface in contact with the surrounding mes-

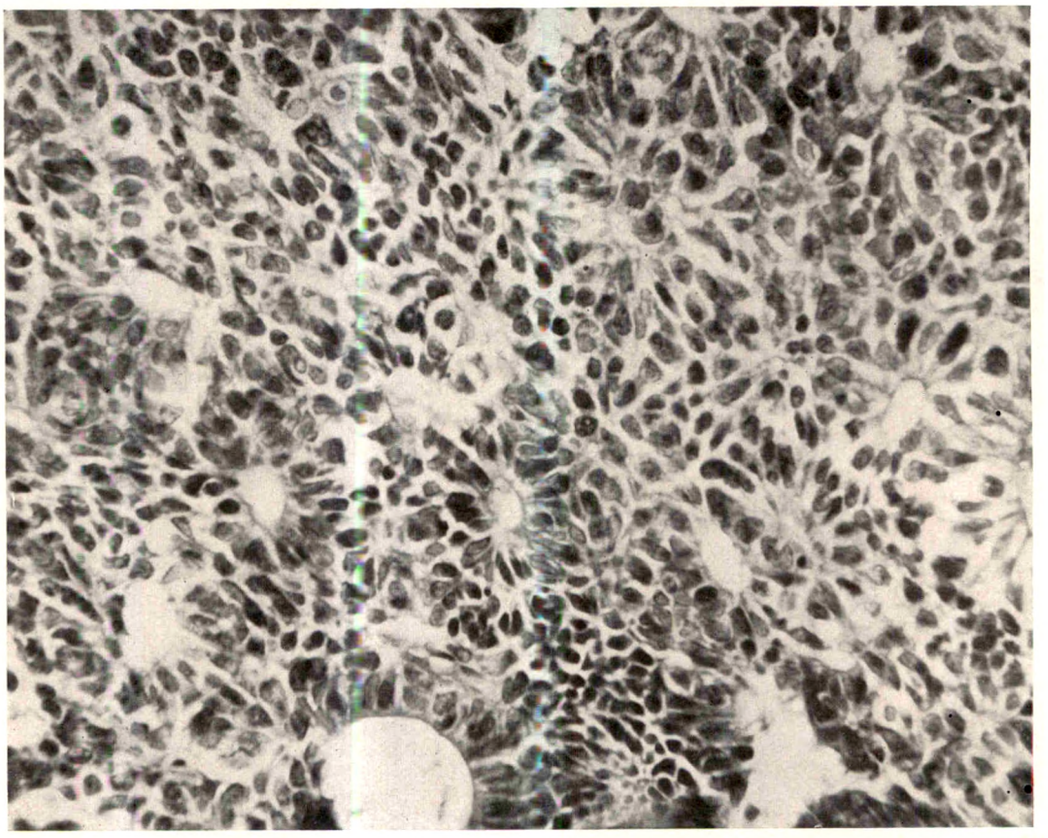


Fig. 8 (Zimmerman). Structures resembling Flexner-Wintersteiner rosettes may be observed in malignant medullo-epitheliomas (hematoxylin and eosin, ×380). (AFIP Neg. 70-8781).

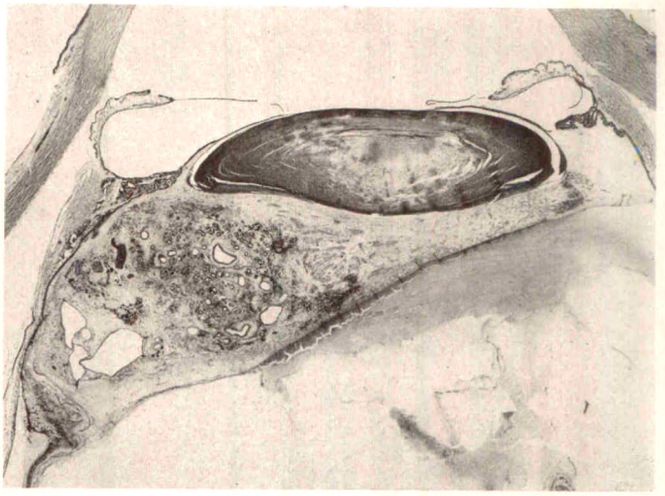


Fig. 9 (Zimmerman). Teratoid medullo-epithelioma. Many tubular and vesicular structures are contained in large retrolental mass of mesenchymal tissue. See Figures 10-12 for details shown at greater magnification (hematoxylin and eosin, ×7). (AFIP Neg. 70-9265).

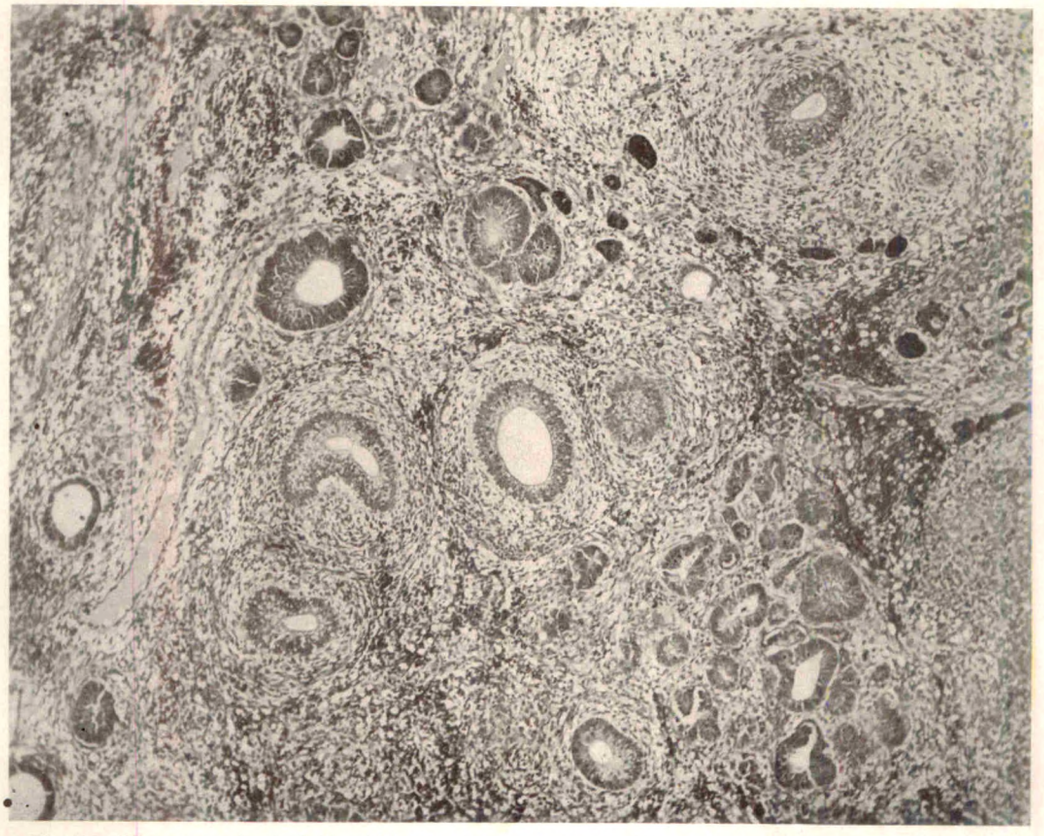


Fig. 10 (Zimmerman). A field within the tumor shown in Figure 9 containing organoid masses of mesenchymal tissue arranged concentrically about tubular structures reminiscent of the primary optic vesicle (hematoxylin and eosin, ×60). (AFIP Neg. 70-8375).

enchyme (Fig. 10). The latter, however, appeared to be clearly oriented concentrically about the medullary epithelium. Within this mesenchyme one could sometimes find bundles of larger, plumper spindle-shaped and straplike cells containing abundant eosinophilic cytoplasm (Fig. 11). These bundles were reminiscent of myotomes, and upon closer scrutiny, well-differentiated skeletal muscle cells containing typical cross-striations could be seen among them (Fig. 12).

In the first case of this sort that came to our attention, it was the presence of large ganglioform cells that stimulated special interest.[28] We were trying to prove to our own satisfaction that the cells were truly ganglion cells, but we were having no success. Finally, electron microscopy was used, even though it was necessary to retrieve tissue from the paraffin block for examination of the cells in question. Instead of providing support for the belief that the ganglioform cells were neurons, electron microscopy proved that they were, in fact, muscle cells with the typical well-differentiated banding of mature rhabdomyoblasts.[29] Even before our electron microscopic study of that tumor was completed we received another that was even stranger in several respects. The entire retina was detached and incorporated in a large mass that involved the ciliary body and iris (Fig. 13). Microscopic examination revealed a remarkably haphazard mixture of neuroepithelial elements, myxoid mesenchymal tissue, and bands of long, plump, spindle-shaped cells (Fig. 14) containing abundant



Fig. 11 (Zimmerman). Another field from the tumor shown in Figure 9 in which bundles of plump spindle-shaped cells (arrows) resembling a myotome are contained in the mesenchymal tissue surrounding the structure lined by medullary epithelium (hematoxylin and eosin, ×60). (AFIP Neg. 70-8374).

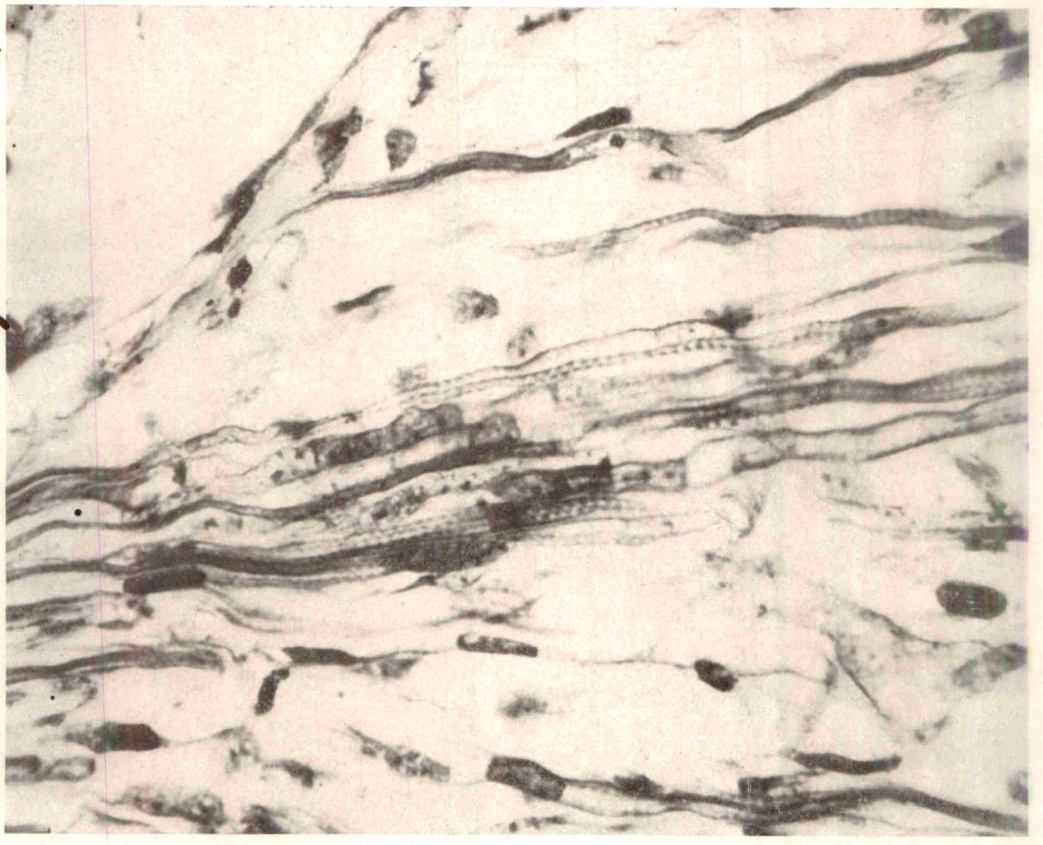


Fig. 12 (Zimmerman). The plump spindle-shaped and straplike cells contained in the mesenchymal tissue of the tumor shown in Figures 9-11 are well-differentiated rhabdomyoblasts exhibiting the typical cross-striations of skeletal muscle cells (phosphotungstic acid-hematoxylin stain, ×525). (AFIP Neg. 70-9149).

eosinophilic cytoplasm in which one could readily see, even without the aid of special stains, the typical cross-striations of skeletal muscle cells (Fig. 15). With appropriate stains one could see a greater number of cells containing such cross-striations (Fig. 16), and even in the loose myxoid mesenchymal tissue one could establish that some of the stellate cells were actually rhabdomyoblasts, thus presenting a picture similar to what one sees in embryonal rhabdomyosarcoma.

In retrospect, the large ganglioform cells (a few of which were also observed in our second case) should have been suspected of being rhabdomyoblasts because we have frequently seen similar cells in rhabdomyosarcomas of the orbit and in other locations. They had the typical concentric cytoplasmic laminations produced by their highly organized myofibrils; they stained intensely with a deep brick-red color with Masson's trichrome stain; and they were rich in glycogen (intensely PAS-positive except after treatment with diastase). Nissl preparations and Bodian stains had failed to provide support for the original notion that these were ganglion cells; yet we did not suspect that these ganglioform cells might be rhabdomyoblasts until we saw them by electron microscopy. From this experience we should learn several lessons. The first is to be more objective. We failed to suspect that the ganglioform cells might be rhabdomyoblasts, not because they didn't have the characteristics of such cells but because their intraocu-

lar location and their association with a neural neoplasm served to effectively eliminate such a possibility from even being considered at our conscious level of differential diagnosis. The second is to "beware of the obvious" and become imaginative. How much are we overlooking every day because our stereotyped thinking doesn't permit us to imagine other possibilities? Finally, the experience again illustrates the potential diagnostic value of electron microscopy. Even when one hasn't had the opportunity to prepare the tissue properly for electron microscopy initially, it is still possible to obtain meaningful (sometimes, as in the present case, crucially diagnostic!) information by retrieving tissue from the paraffin block and then reprocessing it for electron microscopy.

Having had in quick succession these several medullo-epitheliomas with a rhabdomyoblastic component, we naturally began to wonder how often we had overlooked such a component in the past, and we also wondered about the possibility that similar tumors might occur intracranially. With regard to the first consideration, I immediately recalled a case that I used for illustrations in a chapter I prepared for Ackerman's Surgical Pathology.[30] In that case, a huge intraocular medullo-epitheliomatous tumor that contained many large islands of hyaline cartilage, some of which suggested sarcomatous change, also had clusters of very large cells with abundant eosinophilic cytoplasm and large vesicular nuclei containing prominent nucleoli. These cells had always been suspected of being ganglion cells, but their identity had never really been established. Unfortunately, we still don't know whether these cells are rhabdomyoblasts because the original tissue, processed in celloidin, was used for study sets, and I have not been able to retrieve satisfactory tissue for further study by light or electron microscopy. In my recent review of all our ciliary body tumors,[10] I did come across several other cases in which strap cells, racquet cells, or ganglioform cells suggestive of rhabdomyoblasts were present, but in those old cases I was never able to establish conclusively the presence of a rhabdomyoblastic component. Among our more recently accessioned cases, however, we now have a total of four specimens in which we have been able to demonstrate rhabdomyoblasts with typical well-differentiated cross-striations. In three of the four tumors, the cross-striations are demonstrable even in sections stained by hematoxylin and eosin, but in one case they were identified only by electron microscopy.[28]

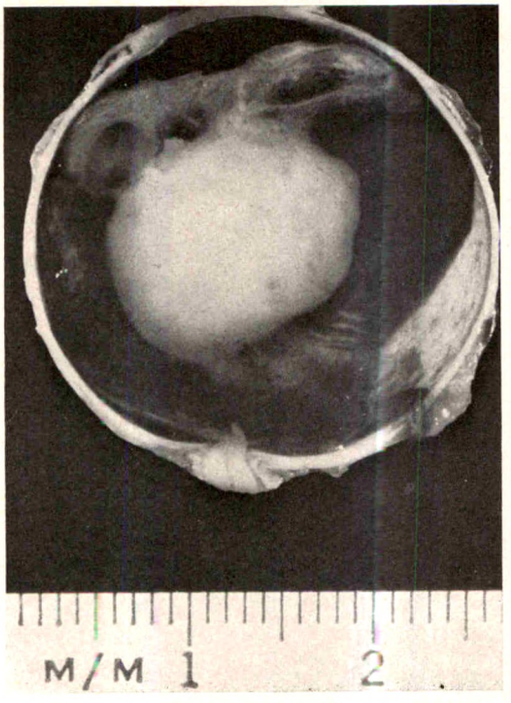



Fig. 13 (Zimmerman). Teratoid medullo-epithelioma. The entire retina and the ciliary body are incorporated into a large mass of neoplastic tissue. See Figures 14-16 for some of the histopathologic features of this unusual tumor. (AFIP Neg. 69-8030-5).

With regard to the occurrence of a rhabdomyoblastic component in other tumors of the central nervous system, a number of cases have been reported.[31-36] Most have been considered cerebellar medulloblastomas and have occurred in children. The term "medullomyoblastoma" has been coined for them. Some authors have considered such tu-

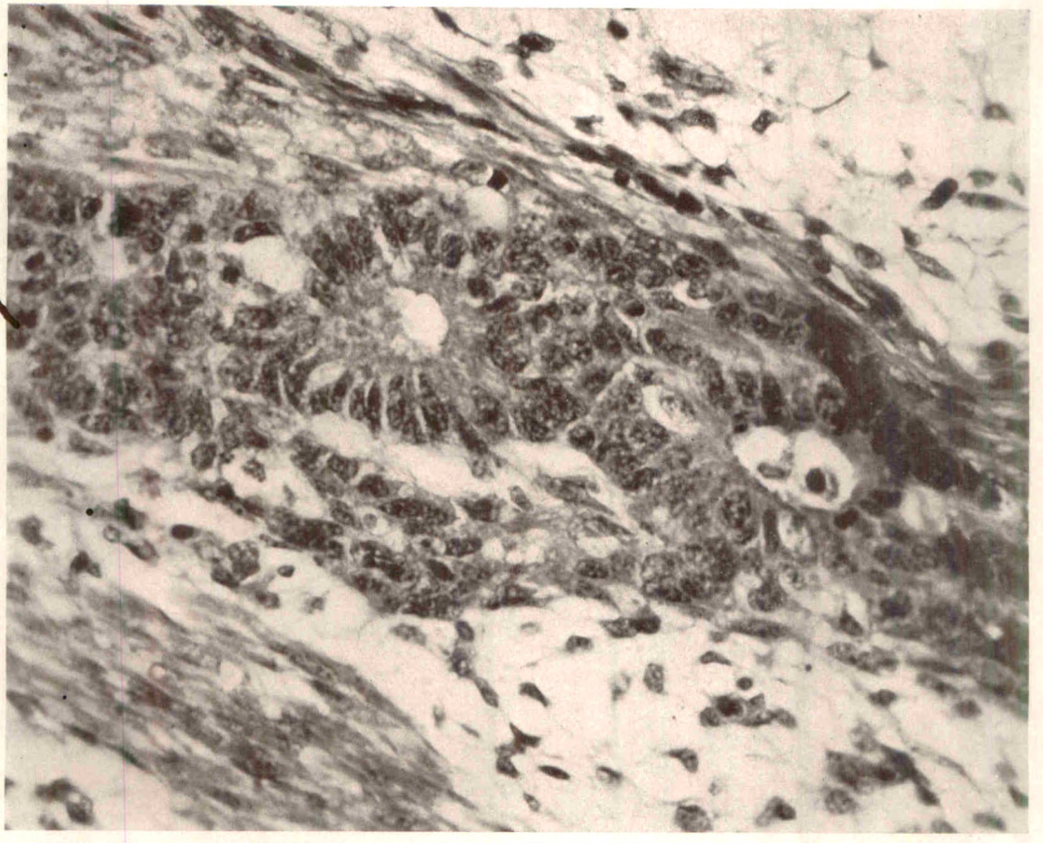


Fig. 14 (Zimmerman). Within the tumor shown in Figure 13 there are numerous neuroepithelial structures intimately associated with loose mesenchymal tissue and bundles of plump spindle-shaped and strap-like cells (hematoxylin and eosin, ×380). (AFIP Neg. 69-9796).

mors as being teratomatous; others have suggested that they are immature leptomeningeal neoplasms (sarcomas) of the posterior fossa. According to Goldman,[35] the primary tumors of the central nervous system containing rhabdomyosarcomatous elements fall into three groups: a teratoid group, in which the sarcomatous elements are associated with medulloblastoma; primary sarcomas that are probably of meningeal origin; and his own "unique" case, in which the sarcoma appeared to be derived from the mesodermal tissue associated with the vascular supply of a primary glioma. Experimentally, medulloblastomas of the cerebellum have been produced in mice, and in some of the resultant neoplasms, cells of a sarcomatous nature have been identified among the neuroblastic elements, though no evidence of rhabdomyoblastic differentiation was described.[37]

The question also arises as to the histogenesis or embryogenesis of the cartilage and skeletal muscle observed in association with these medullo-epitheliomas. Several suggestions may be made, but we have no absolute proof that any one is the correct answer. First, as Verhoeff pointed out, and as I have repeatedly observed in our cases, the tumor usually has some vascular stroma. Often there is a large vascularized mesenchymal retrolental mass that resembles and probably is hyperplastic primary vitreous. The vessels entering this mass in the posterior chamber can often be shown to have had their origin from the stroma of the ciliary body, entering through a colobomatous defect in the continuity of the pigmented and nonpigmented

layers of ciliary epithelium. Thus, one must consider the possibility that heteroplasia took place in the mesodermal tissue contained in the persistent hyperplastic primary vitreous. As we have recently reported,[38] one may see heteroplastic adipose tissue in persistent hyperplastic primary vitreous, but to date we have not seen either skeletal muscle or cartilage in such cases, nor have we seen adipose tissue in our teratoid medullo-epitheliomas. Cartilage, however, is a well-known constituent of the colobomatous defects in the severely microphthalmic eyes of babies born with a 13-15 trisomy,[39] and it may rarely be seen in unilaterally malformed eyes not associated with any systemic anomaly or chromosomal disorder.[40] Thus a most likely possibility is that the cartilage and skeletal muscle observed in association with these medullo-epitheliomas are derived from mesoderm entering through a colobomatous defect in the medullary epithelium.

Another distinct possibility is the origin of these tissues from the neural ectoderm itself. At least one example of the origin of striated muscle fibers from the neural ectoderm is well established. In birds and reptiles, the pupillary muscles have the typical cross-banding of skeletal muscle fibers.[41] Old embryologic studies indicated that these muscles are derived from the medullary epithelium,[42] just as are the smooth iridic muscles of man and most other species. Recently the embryologic development of these "skeletal" muscle cells from the medullary epithelium at the rostral margin of the optic cup in the chick

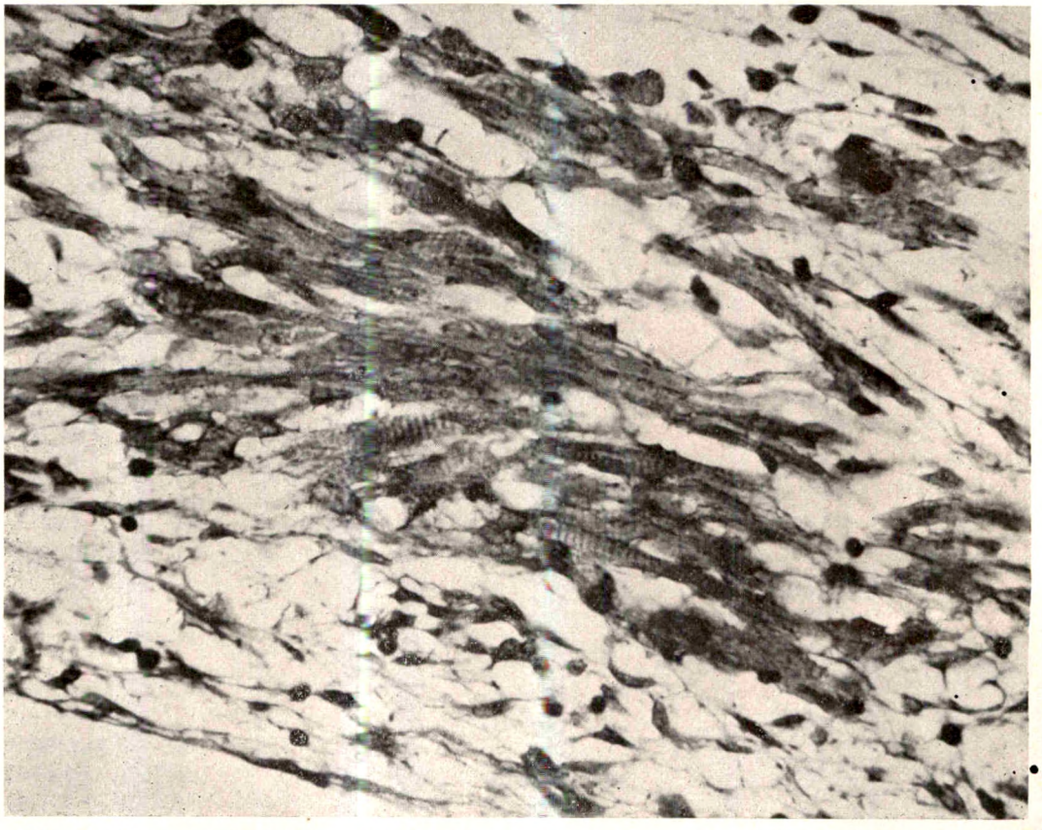


Fig. 15 (Zimmerman). Rhabdomyoblastic differentiation of many cells contained within the loose mesenchymal tissue of the tumor shown in Figures 13 and 14 is evident even without the aid of special stains (hematoxylin and eosin, ×380). (AFIP Neg. 70-7862).

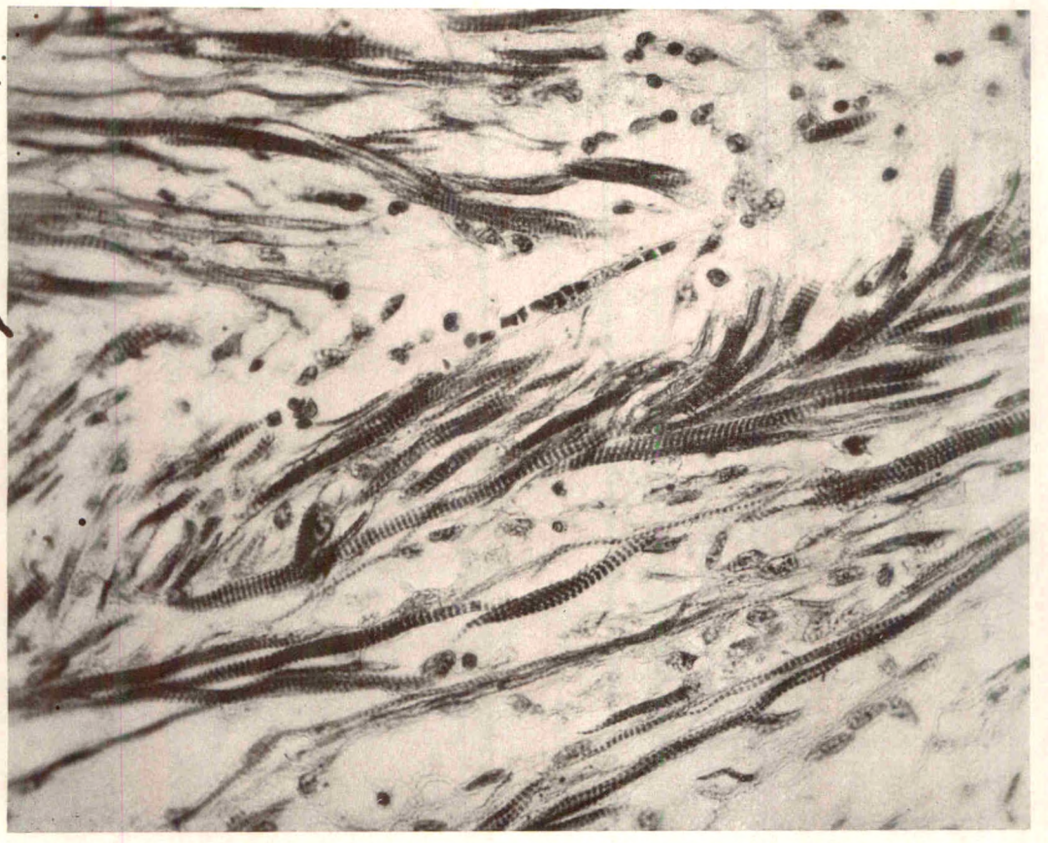


Fig. 16 (Zimmerman). The typical cytoplasmic cross-striations of skeletal muscle are demonstrated much more vividly with the phosphotungstic acid-hematoxylin stain (×305). (AFIP Neg. 69-9805).

has been under investigation by light and electron microscopy in our laboratory, and we can confirm the fact that the neural ectoderm does have the potential for the production of rhabdomyoblasts.[43] In some of our tumors, the extremely intimate relationship of rhabdomyoblasts to neuroepithelial elements suggests the possibility that the two cell types may have arisen from a common precursor.

Still another possibility remains to be considered. According to some embryologists, the mesenchyme should be considered in a functional sense rather than as a genetic entity. It can be derived from various epithelia regardless of their blastodermic layer of origin. In the region of the head, especially, much of the mesenchyme is derived from the neural crest. According to Starck,[44] this neuroectodermal mesenchyme contributes to the formation of cartilage, bone, and odontoblasts and may be termed the "mesectoderm." The cephalic neural crest is also believed to give rise to melanocytes, Schwann cells, neuroblasts, and ganglion cells of the sympathetic nervous system and to leptomeningeal cells. In tissue culture, cells from the neural crest have been observed to differentiate along several pathways, and when grown in the presence of entodermal cells from the pharyngeal area, they produce cartilage.[45] Thus it seems possible that the loose mesenchymal tissue contained in the stroma supporting the medullo-epitheliomatous elements may actually be mesectoderm and that the islands of hyaline cartilage may be derived from such neuro-ectodermal tissue. I have not, however, come across any refer-

ence to the mesectoderm giving rise to skeletal muscle, though, as I have already mentioned, it is well established that in birds and reptiles the neuro-ectoderm can give rise to striated muscle.

Finally, before closing let me say that the knowledge that a sarcomatous orbital tumor may have originated inside the eye can be useful for the surgical pathologist. Recently we were sent in consultation a chondrosarcomatous neoplasm in the orbit of a nine-year-old boy whose eye had been enucleated three years earlier—allegedly for retinoblastoma. When we were able to study the original ocular tumor, our suspicions proved to be correct. The intraocular tumor was not a retinoblastoma but, rather, a teratoid medullo-epithelioma containing a rhabdomyosarcomatous component. We were not able to demonstrate a cartilaginous component in the two blocks of tissue obtained from the eye, but we nevertheless have no doubts that the orbital chondrosarcoma represents a recurrence of the original malignant teratoid medullo-epithelioma. In this connection, the case of intraocular chondrosarcoma in a cat reported by Barron and Saunders[46] is of interest. I have studied that tumor very carefully and believe it, too, belongs in the category of malignant teratoid medullo-epitheliomas, but because the chondrosarcomatous component has so overgrown everything else inside the eye, it is difficult to be certain of this interpretation.

## Summary

Although Verhoeff made an incredibly detailed and accurate histopathologic study of the tumor he described in 1904, the name he chose for it ("terato-neuroma") seems inappropriate because the tumor was neither truly teratoid nor neuronal. In retrospect, and with the large experience we and others have had since Verhoeff's time, it is apparent that his tumor was a sort of prototype of the pure medullo-epithelioma, an embryonic neoplasm containing structures resembling the medullary epithelium of the optic vesicle and its derivatives. Other medullo-epitheliomas that have since been studied contain, in addition, heteroplastic elements—tissues not normally observed in the eye—and may therefore be called teratoid medullo-epitheliomas. Brain, cartilage, and rhabdomyoblasts are the most readily recognized heteroplastic elements observed in these teratoid medullo-epitheliomas.

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# EARLY EFFECTS OF SINGLE AND REPEATED DOSES OF L-EPINEPHRINE IN MAN

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In a recent review of the mechanism of action of the adrenergic drugs in glaucoma, Sears[1] distinguished three effects of topical L-epinephrine upon the maintenance level of intraocular pressure: (1) an early decrease in pressure partly related to a decrease in aqueous production, (2) an early increase in outflow facility overlapping the decrease in aqueous production, and (3) a progressive increase in outflow facility with continued L-epinephrine medication.

In 1962[2] and again in 1964,[3] Kleis, Barkstrom and I reported on early increases in outflow facility in patients with ocular hypertension or primary open-angle glaucoma after single doses of L-epinephrine. These observations were extended and partly confirmed by other investigators. The present paper provides a fuller picture of the early effects of L-epinephrine based on new measurements and intrasubject comparisons with the effects of other ocular hypotensive agents.

## MATERIALS AND METHODS

The patients who participated in this study came from a group with ocular hypertension or primary open-angle glaucoma which has been under observation for several years. The status of their aqueous dynamics has been followed regularly in the outpatient department and this has yielded base line values for pressure and outflow facility ($P_b$, $C_b$) with only slight interference with these patients' normal daily activities. The base line values have been checked at suitable intervals, usually every six months. In general, the diurnal pressure pattern has been that of a high between 7 and 10 A.M. and a low in the evening. During the early morning hours the applanation pressures have been consistently higher than 24 mm Hg. Outflow facility (C), as determined by conventional tonography using Friedenwald's 1955 tables, has not varied significantly between 7 A.M. and 4 P.M.; a few of the patients have shown an increase in C between 7 and 10 P.M.

By repeated paired Schiøtz readings these patients' ocular rigidities were found to lie between 0.0160 and 0.0260. As shown also by other investigators (Lee,[4] Tarkkanen and Karjalainen,[5] Criswick and Drance[6]), during the phases studied, L-epinephrine does not exert a demonstrable effect on ocular rigidity.

L-epinephrine was routinely administered in a single drop of a 2% aqueous solution (containing about 1.02 mg of epinephrine base) between the hours of 7 and 9 A.M. In most parts of the study the applications were made to both eyes, the main reason being that a few instances of possible contralateral effects had been observed after unilateral surface instillation of L-epinephrine. Another reason was that in the majority of patients the abnormality of aqueous dynamics was asymmetrical which made the fellow eye less valuable as a control and more valuable as a test subject.

Pilocarpine in varying dosage was the only previously administered hypotensive medication, and in patients who had received this drug, a minimum of three days was allowed to elapse for evanescence of its effect before L-epinephrine was started.

Observations during the early part of the study suggested variations in the test procedure. The study, therefore, has yielded sev-

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eral series of observations derived from several different groups of patients, all fairly well matched with regard to age, baseline pressure and outflow facility, and prevalence of visual field defects.

*Test procedures*—All measurements were made with certified mechanical or electronic (V. Mueller) tonometers of the Schiøtz type. The test procedures were as follows:

*Series* 1—Pressure readings were taken hourly from 8 A.M. until 4 P.M. for three consecutive days, a control day, a treatment day, and a post-treatment day. L-epinephrine was administered after the 8 A.M. reading on the treatment day.

*Series* 2—Pressure readings were taken hourly from 8 A.M. until 12 noon for five consecutive days the first three of which were control days. L-epinephrine was administered after the 8 A.M. reading on the fourth day. Tonographies were performed each day shortly after the 12 noon pressure reading.

*Series* 3—Pressure readings were taken hourly from 8 A.M. until 12 noon for five consecutive days the first two of which were control days. L-epinephrine was administered after the 8 A.M. reading on the third day. Tonographies were performed each day shortly after the 12 noon reading.

*Series* 4—Pressure readings were taken hourly from 8 A.M. until 12 noon for three consecutive treatment days (the patient receiving a single dose of the drug after each 8 A.M. tonometry). This was followed by 10 days of rest, after which the whole course was repeated twice.

*Series* 5 *and* 6—Repeated tonometries and tonographies were performed between 11 A.M. and 1 P.M. on patients receiving two self-administered 1-2 drop doses of epinephrine daily for one week (Series 5), or for three weeks (Series 6).

For the same length of time and in rotation the last group of patients was also placed on two other hypotensive medications, pilocarpine 4% and echothiophate 0.25%. Within 18 months each of these therapeutic regimens was repeated at least once and in most patients twice, allowing three weeks for evanescence of the effects of L-epinephrine and echothiophate. Some of the patients (Series 6) required acetazolamide for pressure control during the evanescence periods.

## Results

Hourly pressure measurements after a single dose of L-epinephrine administered at 8 A.M. showed variations in individual response during the early phases. A few eyes passed through a mild hypertensive phase, while in others a drop in pressure was recorded at the end of the first hour. These individual variations were similar in pattern and degree to those reported by Richards and Drance.[7]

When measurements were combined into means, the patients in Series 1 (Table 1) showed a drop in pressure that was gradual and reached a maximum four hours after the early morning treatment. Lower pressures continued during the afternoon and were still clearly demonstrable the next

TABLE 1

THE TIME-COURSE OF THE EFFECT ON PRESSURE OF A SINGLE DOSE OF L-EPINEPHRINE
(Series 1, n = 8, arithmetic means)

| Days | Hours | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A.M. | | | | P.M. | | | | |
| | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 |
| Control | 28.4 | 26.5 | 27.8 | 27.8 | 28.0 | 26.5 | 23.2 | 24.5 | 24.5 |
| Treatment | 26.5* | 25.9 | 24.8 | 23.2 | 20.8 | 20.0 | 19.6 | 20.0 | 20.5 |
| Post-treatment | 25.8 | 24.2 | 23.1 | 23.9 | 25.3 | 23.6 | 22.8 | 24.0 | 25.4 |

* Time of treatment.

TABLE 2

EFFECT OF A SINGLE DOSE OF L-EPINEPHRINE ON PRESSURE AND OUTFLOW FACILITY IN OCULAR HYPERTENSION OR PRIMARY OPEN-ANGLE GLAUCOMA
(Series 2, n = 10, arithmetic means ± S.E.)

| | Control Days | | | Treatment Day (Day 4) | Post-treatment Day (Day 5) |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | | |
| Mean morning pressure in mm Hg | 27.1 ± .94 | 26.4 ± .75 | 25.9 ± .87 | 21.4 ± .53* | 19.5 ± .44* |
| Outflow facility in μl/min/mm Hg | .103 ± .011 | .114 ± .012 | .119 ± .009 | .186 ± .015* | .173 ± .014* |

* $P < .01$

day. This pointed toward the early afternoon hours of the treatment day as the time of the maximal pressure effect of single doses of L-epinephrine. Procedures used in Series 2 and 3 were, therefore, designed to combine tonography about five hours after treatment with hourly tonometries during the morning. To get more information about the optimal length of the control and post-treatment periods, the control period was extended to three days preceding drug administration in Series 2 and the post-treatment observation period extended to three days in Series 3. The hourly morning pressure readings, excluding the first reading on the treatment day, were combined into means for the individual eye and the individual day.

The data thus obtained (Tables 2 and 3) are indicative of insignificant changes from one control day to the next, of a significant mean pressure drop from the last control day to the treatment day and of an even more significant mean pressure drop from the last control to the post-treatment day. Lower mean pressures than on the last control day still prevailed on the second day after treatment. Since the results in Series 2 and 3 were in essentially good agreement, they were combined in Figure 1 for the presentation of the pressure drops in the individual eyes. Both the treatment day and the post-treatment day data show the approximately linear relationship between pressure drop ($\Delta P$) and starting level ($P_b$) that is known

TABLE 3

EFFECT OF A SINGLE DOSE OF L-EPINEPHRINE ON PRESSURE AND OUTFLOW FACILITY IN OCULAR HYPERTENSION OR PRIMARY OPEN-ANGLE GLAUCOMA
(Series 3, n = 12, arithmetic means ± S.E.)

| | Control Days | | Treatment Day (Day 3) | Post-treatment Day (Day 4) | Second Day Post-treatment (Day 5) |
|---|---|---|---|---|---|
| | 1 | 2 | | | |
| Mean morning pressure in mm Hg | 27.4 ± 1.12 | 28.2 ± 1.07 | 24.4 ± 1.34* | 23.0 ± 0.71† | 25.4 ± 1.05 |
| Outflow facility in μl/min/mm Hg | .109 ± .006 | .106 ± .007 | .176 ± .007† | .160 ± .009† | .120 ± .009 |

* $P < .05$
† $P < .01$

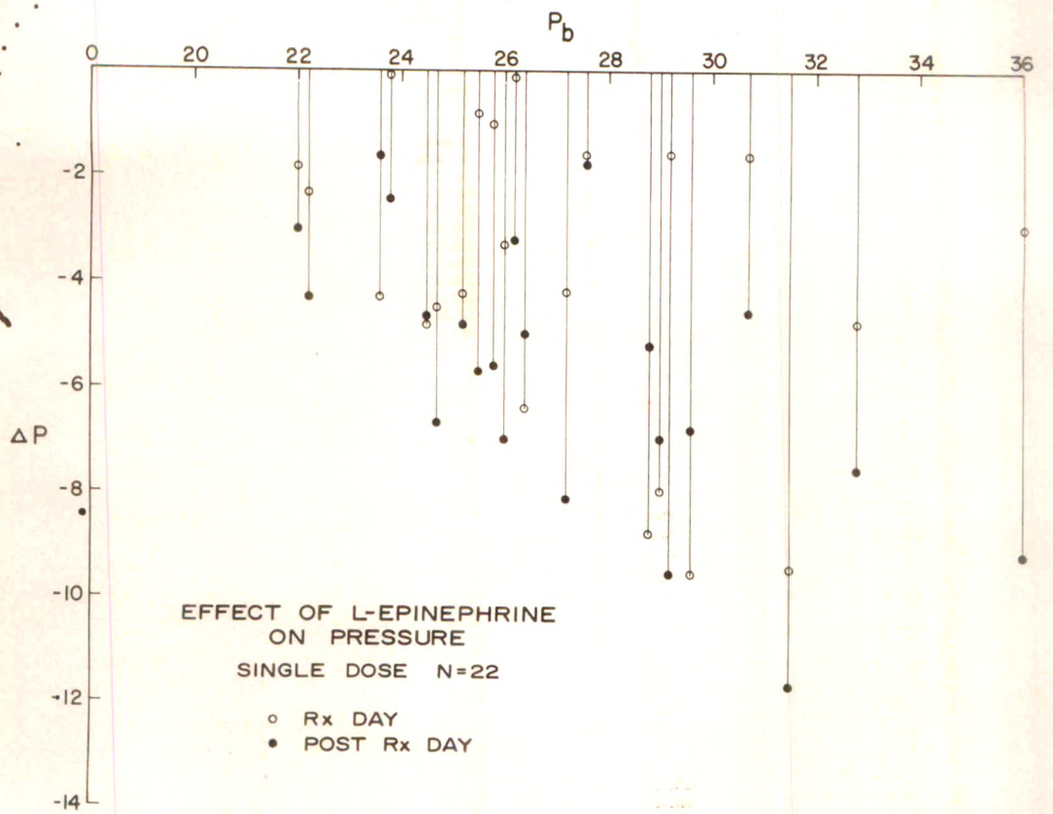



Fig. 1 (Kronfeld). The base line pressures recorded on the abscissa ($P_b$) are the means of hourly morning pressure measurements on the control day preceding the administration of a single dose of 2% L-epinephrine. The ordinates ($\Delta P$) are the differences between $P_b$ and the mean morning pressures on the day of treatment (empty circles) and on the day following treatment (solid circles). The subjects are patients with ocular hypertension or primary open-angle glaucoma (Series 2 and 3).

to apply, within definite limits, to the effects of other hypotensive agents.[8,9] In addition, there is considerable individual variation, with a few eyes standing out by their poor responses.

With the drop in pressure the phenomenon of the early increase in outflow facility is shown in Tables 2 and 3, most pronounced on the treatment day, less so on the post-treatment day, and barely suggested on the second day after treatment. The relationship between base line and drug-response values is made simpler and clearer by conversion of outflow facility into outflow resistance. A linear relationship is known to exist between a pilocarpine-induced drop in resistance ($\Delta R$) and the baseline value ($R_b$).[9-11] In Figure 2 this relationship may also be deduced for single doses of L-epinephrine. There was only one eye that responded poorly in terms of outflow resistance, and in this case it was not associated with a poor pressure response.

Other data regarding single-dose responses were available from Series 4. These patients received single, one-drop doses for three consecutive days, and each three-day course of drug administration on this regimen was repeated three times with 10 days intervening between the courses. The findings on the first day of these courses are shown in Table 4.

### Short-term sustained administration

The effects of L-epinephrine remain es-

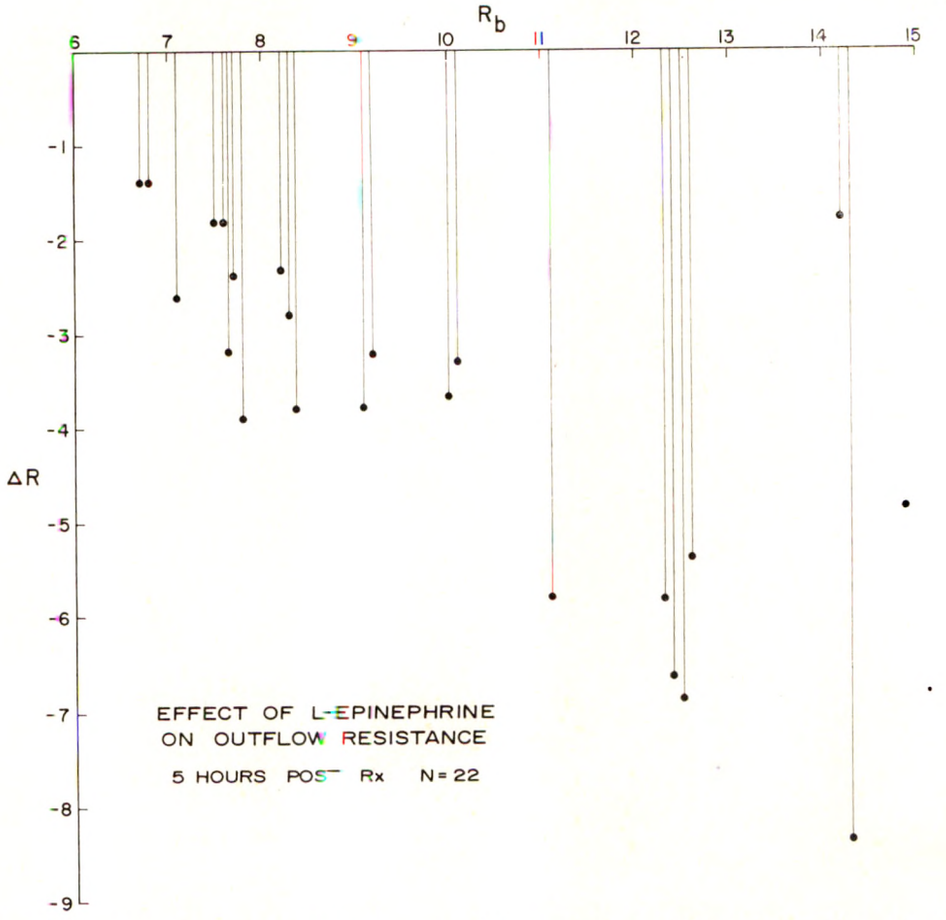



Fig. 2 (Kronfeld). The base line resistances recorded on the abscissa ($R_b$) are the reciprocals of the midday measurements of outflow facility on the control day preceding the administration of a single dose of 2% L-epinephrine. The ordinates ($\Delta R$) are the differences between $R_b$ and the reciprocal of the midday outflow facility on the day of treatment. The subjects are patients with ocular hypertension or primary open-angle glaucoma (Series 2 and 3).

TABLE 4

REPEATABILITY OF THE EPINEPHRINE-INDUCED INCREASE IN OUTFLOW FACILITY SINGLE-DOSE TESTS REPEATED AT 14-DAY INTERVALS

(Series 4, right eyes only, outflow facility in μl/min /mm Hg)

| Subject | Base Line Range | Repeat Tests | | |
|---|---|---|---|---|
| | | First | Second | Third |
| M.B. | 0.11–0.14 | 0.18 | 0.19 | 0.19 |
| A.A. | 0.10–0.15 | 0.20 | 0.15 | 0.20 |
| F.M. | 0.12–0.15 | 0.31 | 0.27 | 0.28 |
| C.L. | 0.13–0.19 | 0.31 | 0.24 | 0.25 |
| M.C. | 0.07–0.12 | 0.23 | 0.22 | 0.20 |
| C.L. | 0.06–0.09 | 0.21 | 0.23 | 0.15 |

TABLE 5

COMPARISON OF SINGLE AND REPEATED DOSE EFFECTS
(Series 5, n = 16)

| Subject and Eye | Base Line* | | L-epinephrine 2% | | | |
|---|---|---|---|---|---|---|
| | | | Single Dose | | Two Times Daily for One Week† | |
| | P | C | P | C | P | C |
| S.W. | | | | | | |
| Right eye | 22.0 | 0.130 | 17 | 0.25 | 17 | 0.25 |
| Left eye | 20.0 | 0.130 | 15 | 0.22 | 19 | 0.25 |
| K.M. | | | | | | |
| Right eye | 23.2 | 0.136 | 15 | 0.26 | 16 | 0.21 |
| Left eye | 23.0 | 0.131 | 17 | 0.27 | 21 | 0.25 |
| H.J. | | | | | | |
| Right eye | 20.3 | 0.128 | 16 | 0.26 | 13 | 0.27 |
| Left eye | 20.3 | 0.119 | 15 | 0.24 | 12 | 0.29 |
| C.J. | | | | | | |
| Right eye | 19.0 | 0.110 | 14 | 0.18 | 16 | 0.23 |
| Left eye | 19.0 | 0.130 | 13 | 0.21 | 15 | 0.21 |
| M.R. | | | | | | |
| Right eye | 21.0 | 0.130 | 12 | 0.32 | 12 | 0.30 |
| Left eye | 25.2 | 0.100 | 14 | 0.21 | 18 | 0.25 |
| W.E. | | | | | | |
| Right eye | 21.0 | 0.150 | 18 | 0.30 | 13 | 0.27 |
| Left eye | 18.2 | 0.150 | 17 | 0.29 | 13 | 0.29 |
| G.C. | | | | | | |
| Right eye | 20.0 | 0.088 | 13 | 0.29 | 14 | 0.24 |
| Left eye | 19.8 | 0.093 | 15 | 0.25 | 16 | 0.25 |
| S.F. | | | | | | |
| Right eye | 26.8 | 0.060 | 22 | 0.16 | 16 | 0.15 |
| Left eye | 25.7 | 0.062 | 19 | 0.15 | 18 | 0.14 |

* Means of three or more measurements.
† Means of two measurements.

sentially unchanged if two instillations per day are continued for one week (Table 5, Series 5). This finding suggested that sustained medication for a limited period might produce a quasi-steady state which would allow repeated measurements that could be combined into truly representative means. This proved to be the case. Four to six measurements during the second and third week of treatment (Series 6) revealed no systematic upward or downward trend and were, therefore, taken to reflect an at least temporary steady state. These measurements are shown in Table 6 as means and ranges for pressure and facility.

Short-term sustained medication elicited, on the whole, somewhat greater responses than the single doses. In the performance of the individual eyes, a nearly linear dependence of the responses upon their baseline values can again be recognized (Fig. 3 and 4). Comparison with the effects of pilocarpine and echothiophate shows that in the dosages used in this study the response pattern for L-epinephrine was fairly close to that of echothiophate (Fig. 5); a distinguishing feature of the pilocarpine effect was the occurrence of slight responses, both in terms of pressure and of resistance (Fig. 6).

## COMMENT

The search for representative indicators of drug effects had to begin with a search for base lines. The base lines chosen for this study were the means of repeated middle-of-the day tonometries and tonographies done in the outpatient department with only minimal interruptions of the patient's normal

TABLE 6

EFFECT OF 2% L-EPINEPHRINE ON PRESSURE AND OUTFLOW FACILITY IN OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA
(Series 6, n = 22)

| Subject and Eye | Base Line | | | | Treatment Twice Daily for Three Weeks | | | |
|---|---|---|---|---|---|---|---|---|
| | P | | C | | P | | C | |
| | Range | Mean | Range | Mean | Range | Mean | Range | Mean |
| A.S. | | | | | | | | |
| Right eye | 27–34 | 32.3 | 0.05–0.08 | 0.060 | 14–17 | 14.8 | 0.13–0.17 | 0.144 |
| Left eye | 27–34 | 31.8 | 0.05–0.08 | 0.065 | 14–17 | 15.2 | 0.14–0.19 | 0.178 |
| G.M. | | | | | | | | |
| Right eye | 23–28 | 26.8 | 0.06–0.11 | 0.077 | 16–17 | 16.7 | 0.18–0.24 | 0.190 |
| Left eye | 23–33 | 30.0 | 0.05–0.10 | 0.077 | 17–21 | 20.2 | 0.19–0.22 | 0.190 |
| S.F. | | | | | | | | |
| Right eye | 25–31 | 26.8 | 0.04–0.07 | 0.060 | 18–22 | 20.0 | 0.11–0.15 | 0.123 |
| Left eye | 25–27 | 25.7 | 0.05–0.07 | 0.062 | 18–22 | 20.8 | 0.10–0.13 | 0.117 |
| D.L. | | | | | | | | |
| Right eye | 25–34 | 26.6 | 0.04–0.10 | 0.089 | 17–19 | 18.0 | 0.16–0.19 | 0.185 |
| Left eye | 22–34 | 24.5 | 0.04–0.10 | 0.089 | 17 | 17.0 | 0.13–0.17 | 0.150 |
| K.F. | | | | | | | | |
| Right eye | 25–28 | 25.6 | 0.06–0.11 | 0.093 | 16–18 | 17.3 | 0.17–0.22 | 0.188 |
| Left eye | 25–29 | 26.2 | 0.06–0.11 | 0.102 | 15–18 | 16.8 | 0.18–0.23 | 0.203 |
| G.L. | | | | | | | | |
| Right eye | 21–29 | 25.4 | 0.07–0.13 | 0.110 | 16–17 | 16.7 | 0.20–0.24 | 0.217 |
| Left eye | 21–28 | 24.3 | 0.07–0.13 | 0.109 | 17 | 17.0 | 0.20–0.24 | 0.227 |
| S.M. | | | | | | | | |
| Right eye | 22–26 | 24.4 | 0.08–0.12 | 0.090 | 15–18 | 15.9 | 0.20–0.22 | 0.207 |
| Left eye | 20–24 | 22.3 | 0.08–0.12 | 0.096 | 15–18 | 15.4 | 0.17–0.20 | 0.175 |
| K.M. | | | | | | | | |
| Right eye | 22–24 | 23.2 | 0.13–0.16 | 0.136 | 15–18 | 16.3 | 0.21–0.27 | 0.230 |
| Left eye | 22–26 | 23.0 | 0.12–0.14 | 0.131 | 17–20 | 18.7 | 0.18–0.23 | 0.227 |
| R.M. | | | | | | | | |
| Right eye | 21–25 | 22.0 | 0.07–0.13 | 0.096 | 16–17 | 16.7 | 0.18–0.25 | 0.185 |
| Left eye | 19–22 | 20.8 | 0.07–0.13 | 0.099 | 14–15 | 15.1 | 0.20–0.31 | 0.205 |
| H.J. | | | | | | | | |
| Right eye | 19–22 | 20.3 | 0.12–0.17 | 0.128 | 15 | 15.0 | 0.26–0.30 | 0.280 |
| Left eye | 19–22 | 20.3 | 0.10–0.13 | 0.119 | 13–17 | 15.0 | 0.23–0.28 | 0.253 |
| G.C. | | | | | | | | |
| Right eye | 18–21 | 20.0 | 0.08–0.10 | 0.088 | 13–15 | 14.0 | 0.23–0.25 | 0.240 |
| Left eye | 18–21 | 19.8 | 0.07–0.12 | 0.093 | 13–16 | 14.0 | 0.23–0.28 | 0.240 |

daily activities. The results of these tonographies are normally distributed with standard deviations of the order of 0.010-0.022 µl/minute/mm Hg.[12]

The new data relating to single-dose effects may be compared with the results of the recent studies by Criswick and Drance,[6] and by Makabe.[13] Despite some differences in technique with regard to magnitude and range of responses, the three studies are in good agreement (Table 7).

In the study by Criswick and Drance,[6] and also that by Makabe,[13] only one eye of each patient was studied, with the fellow eye either serving as control or not participating. Most of the data of the present study are derived simultaneously from both eyes of each patient. Because of the well-known similarity of the parameters of aqueous dynamics in the two eyes of the same subject, the use of both eyes in drug studies may add to the strength of the results at the price of reducing the range of interindividual variations. Because of this potential weakness of the present study, the similarity of its results to those of the other two studies is reassuring.

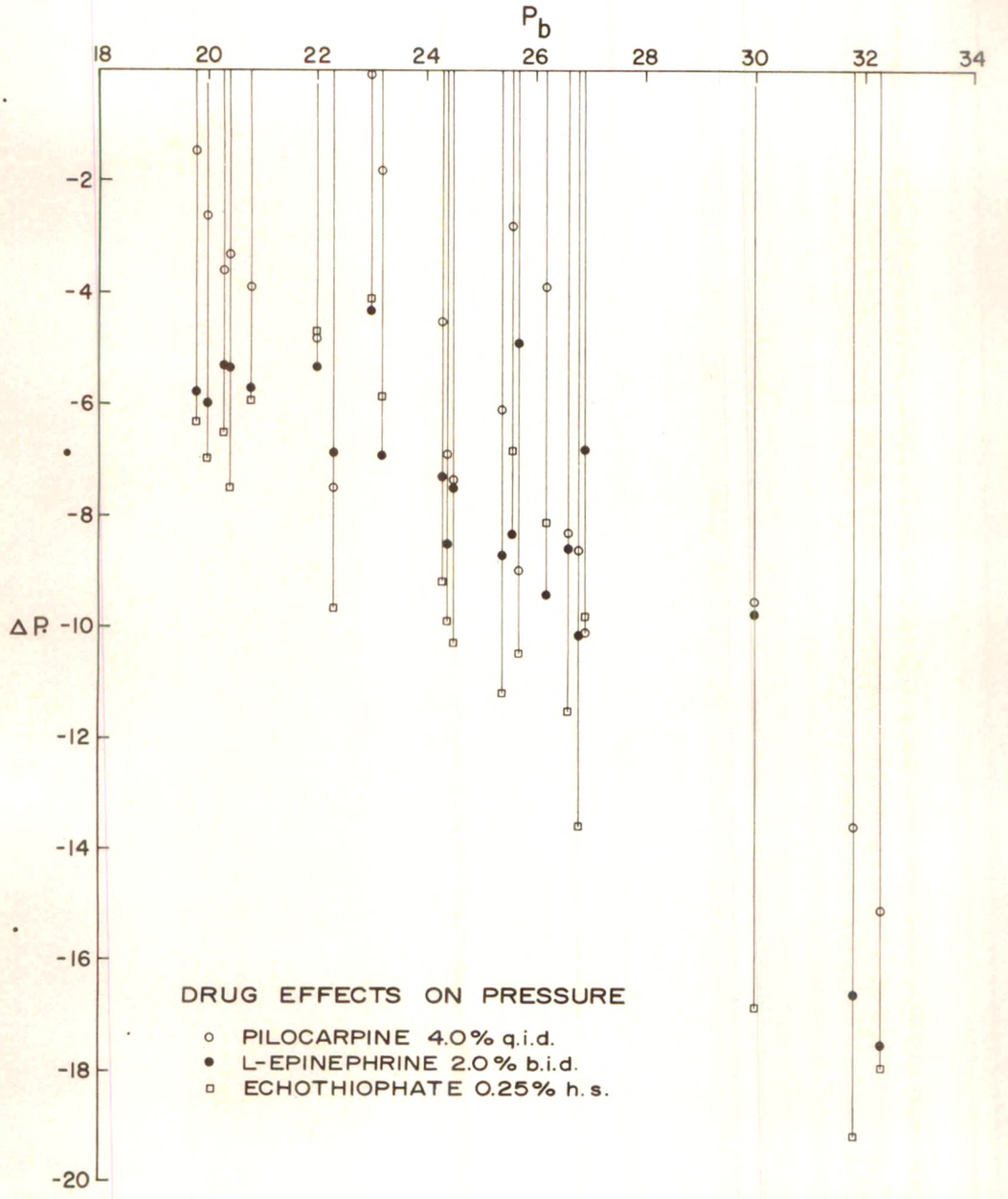



Fig. 3 (Kronfeld). Each vertical line represents the responses of one eye of Series 6. The $P_b$ values on the abscissa are the means of midday pressure measurements without hypotensive medication. The ordinates ($\Delta P$) are the differences between $P_b$ and the means of midday pressure measurements during three-week courses of treatment with the agents indicated in the figure.

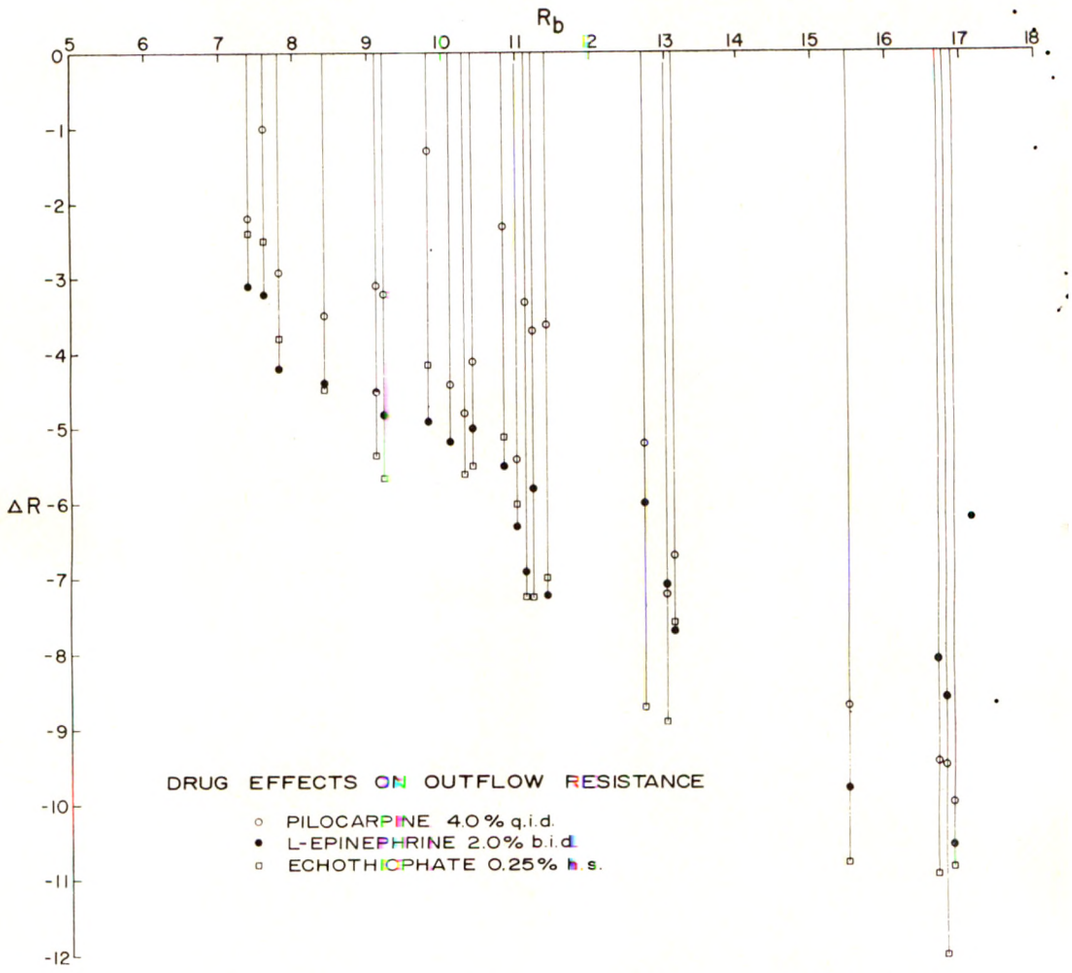



Fig. 4 (Kronfeld). Each vertical line represents the responses of one eye of Series 6. The $R_b$ values on the abscissa are the reciprocals of means of midday measurements of outflow facility without hypotensive medication. The ordinates ($\Delta R$) are the differences between $R_b$ and the reciprocals of means of midday measurements of outflow facility on patients with ocular hypertension or primary open-angle glaucoma (Series 6) during three-week courses of treatment with the agents indicated in the figure.

In the new single-dose data the nearly linear dependence of the pressure and resistance drops upon their respective base line values is in accord with Makabe's study[13] and my own findings in an earlier, unpublished series of cases. This is noteworthy because it brings out a similarity between the effects of L-epinephrine and those of cholinergic hypotensives. The drops in pressure and resistance after single doses could not be correlated with each other, which is in accord with the findings of Criswick and Drance.[6] The lack of correlation suggested significant variations of the other major parameter of aqueous dynamics, the rate of aqueous production. In Makabe's series, the flow rates calculated from the tonographic data appeared to be reduced three hours after single doses in 15 out of 20 glaucomatous eyes. Such effects apparently predominate in normal human eyes (Kupfer,[14] Weekers and associates[15]), and in some forms of ocular disease which will require further study.

In the present single-dose data, no consis-

tent change in the flow rates calculated for the individual eyes could be recognized. The mean facility and pressure responses in Tables 2 and 3 indicate that in the early phase of L-epinephrine effects the gain in facility tends to get ahead of the drop in pressure; this has been interpreted as increased pseudofacility by Duzanec and Leydhecker,[16] and

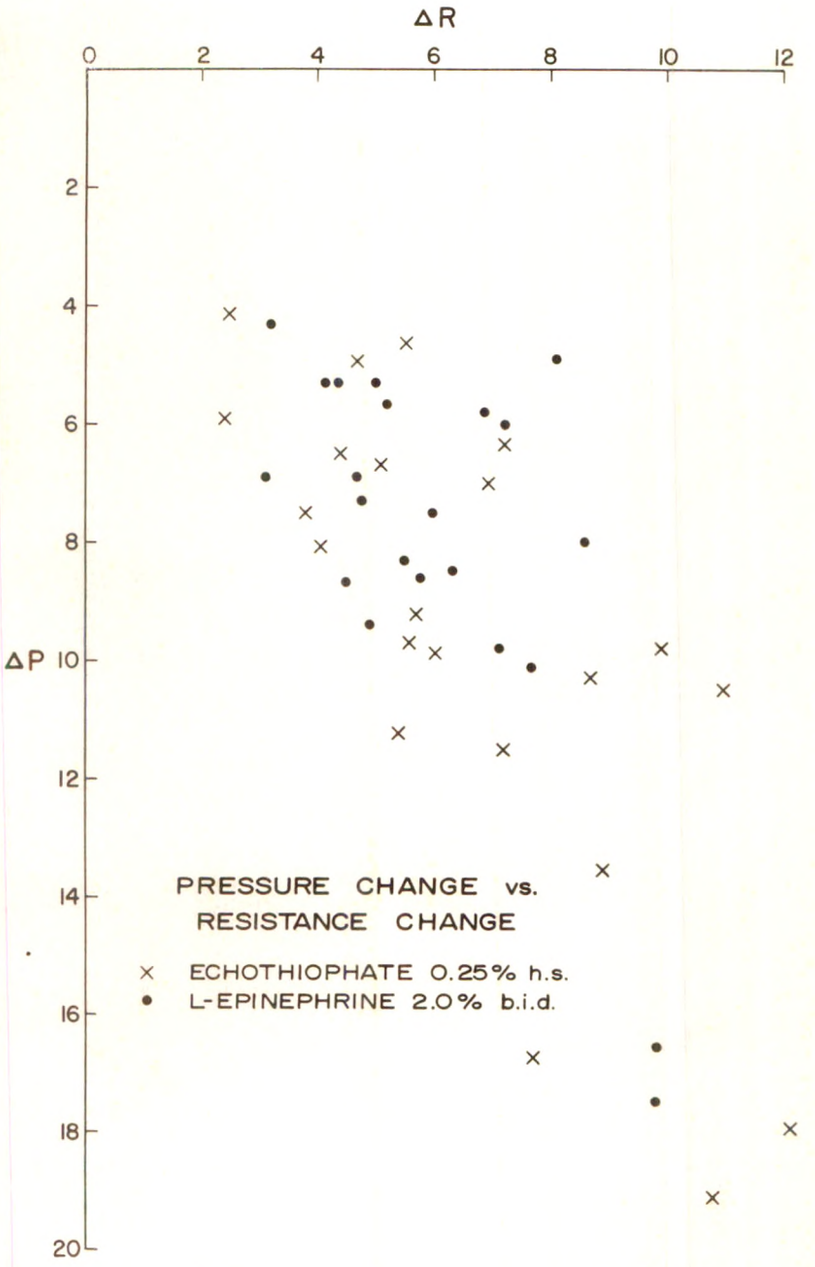



Fig. 5 (Kronfeld). The correlation between the pressure changes and the resistance changes produced by three-week courses of topical hypotensive treatment in patients with ocular hypertension or primary open-angle glaucoma (Series 6).

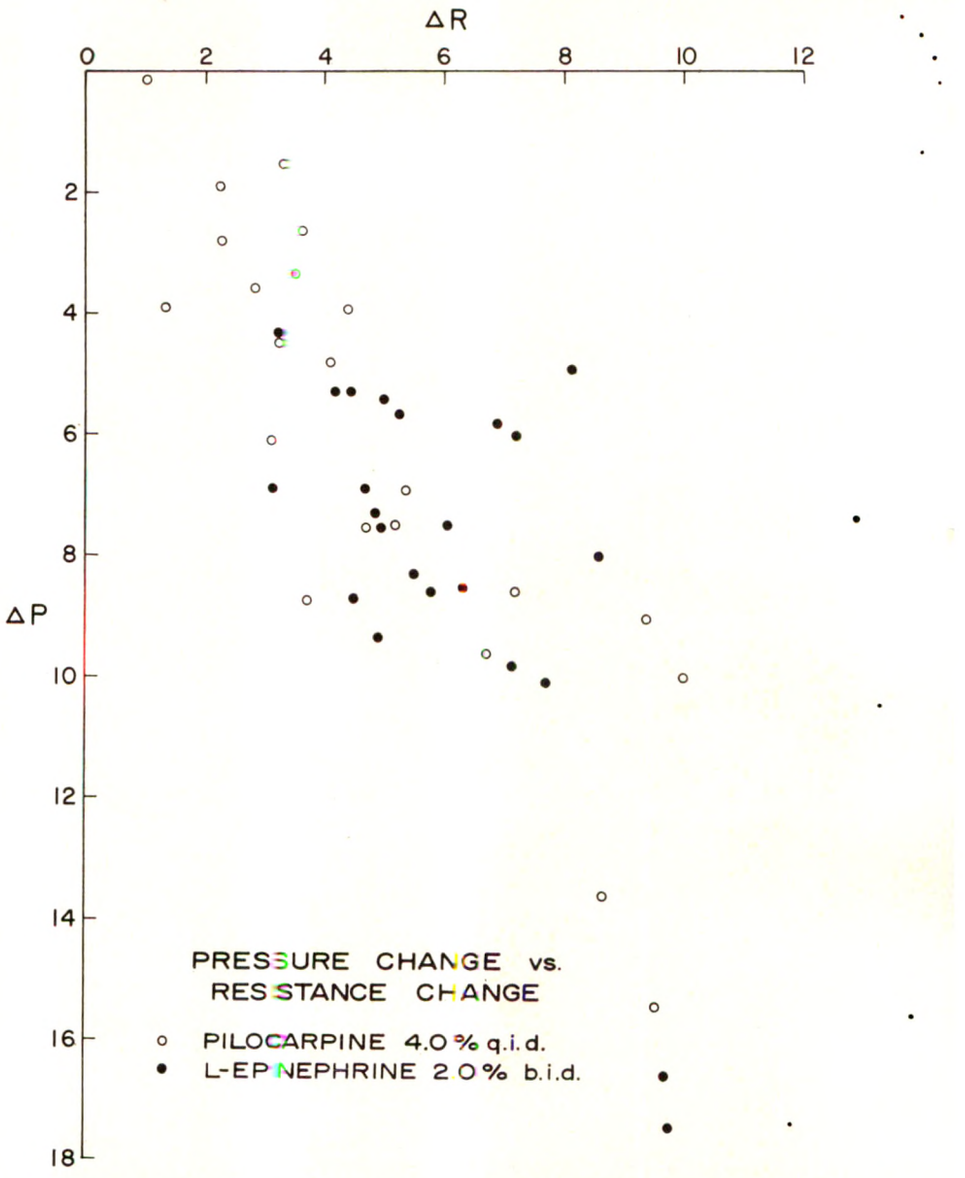



Fig. 6 (Kronfeld). The correlation between pressure and resistance changes produced by three-week courses of topical hypotensive treatment in patients with ocular hypertension or primary open-angle glaucoma (Series 6).

has been observed in monkeys by Bárány.[17] Kupfer's observation in normal human volunteers[14] and Bill's findings in the vervet monkey[18] do not suggest increases in pseudofacility. An initial increase in the rate of aqueous production could explain the discrepancy between outflow facility and pressure.

An increase in the rate of aqueous secretion during the first few hours of L-epinephrine effects was observed by Langham and Weinstein[19] in a sympathetically denervated (that is, supersensitive) human eye.

Abnormalities of sympathetic innervation in glaucoma simplex are by no means clearly established. The usual single dose delivered

TABLE 7

FREQUENCY DISTRIBUTION OF PERCENT OF INCREASE IN OUTFLOW FACILITY IN OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA AFTER SINGLE DOSES OF L-EPINEPHRINE 2%

| Source of Data | Percent Increase | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | Less than −10 | −10 to 10 | 11 to 30 | 31 to 50 | 51 to 70 | 71 to 90 | 91 to 110 | Greater than 110 | |
| Criswick and Drance[6] | — | 2 | 4 | 3 | 5 | 5 | — | 5 | 24 eyes |
| Makabe[13] | 2 | 3 | 3 | 3 | 4 | 1 | 2 | 2 | 20 eyes |
| Present study (Series 2 and 3) | — | — | 3 | 5 | 5 | 4 | 2 | 3 | 22 eyes |

to the eye in the present study (one drop of 2% solution equivalent to about 1 mg of L-epinephrine) is so large in terms of human physiology that initial enhancement rather than the typical inhibition of some aspect of aqueous secretion is conceivable. This could explain the discrepancy between outflow and pressure during the first few hours of the ocular effects of L-epinephrine.

Turning to the effects of sustained L-epinephrine administration, the results in the subjects in Series 6 (Table 6) probably represent the most solid indicators of the early effects of the drug which have emerged from the present study. With regard to magnitude and range of the percent of facility increases, Series 6 differs markedly from the single-dose series 2 and 3. One obvious reason is that the participants in the single-dose studies were selected from a group of patients with ocular hypertension or those with primary open-angle glaucoma whose response to L-epinephrine, at the time of selection, was not known. This group could, and actually did, include poor responders to L-epinephrine. For the three-week sustained administration study (Series 6), some degree of responsiveness to L-epinephrine and to the other drugs was a necessary requirement, so known non-responders were eliminated.

In Series 6, too, there is a nearly linear relationship between the drug-induced resistance and drops in pressure and their base line values (Figs. 4 and 5). Because of the strong correlation between the responses of the patients' two eyes to the drugs used in this study (Fig. 7), it was felt that the sample (Series 6) would become more representative of its population if only one eye of each patient was used in computing the correlation coefficients. This computation for left eyes only (the eyes first tested) yielded correlation coefficients of 0.82 for the L-epinephrine-induced $\Delta P$ versus $P_b$ and of 0.92 for the corresponding $\Delta R$ versus $R_b$, both significant at the 1% level.

In the same sample, a correlation between drops in resistance and in pressure could be demonstrated in a strength of 0.64 for the effects of L-epinephrine and of 0.73 for echothiophate (both significant at the 5% level). Both of these correlations could be made stronger if corrections were applied to the large pressure drops which occurred from starting levels well outside the range of linear relationship between $\Delta P$ and $P_b$.

A search for epinephrine-induced changes in the rate of aqueous production was made by comparing the flow rates calculated from the individual tonographies done under the effect of short-term L-epinephrine therapy with the corresponding base line values. Both sets of values varied within such wide limits for the individual eyes that no consistent effect of the drug on flow rate could be recognized.

Flow rates calculated from the mean pressures and facilities of Table 7 also failed to demonstrate an overall trend toward lower aqueous production rates under short-term epinephrine therapy. In only seven of the 22 eyes listed in Table 7 did the relationship between the rise in facility and the drop in pressure suggest greater than 15% suppression of aqueous production. The dominant effect of epinephrine observed in the present study was clearly the improvement in outflow facility.

### Short-term versus long-term therapy

In Table 8 the two long-term series of Becker and associates[20,21] and the left eyes of the present Series 6 are compared with regard to the percent of improvement in outflow that occurred under L-epinephrine medication. Since in all probability the three series did not differ materially with regard to the condition of the patients' eyes, the gross difference shown in Table 8 (and proved significant at the 0.01 level by the Wilcoxon rank sum test) suggests a rather general

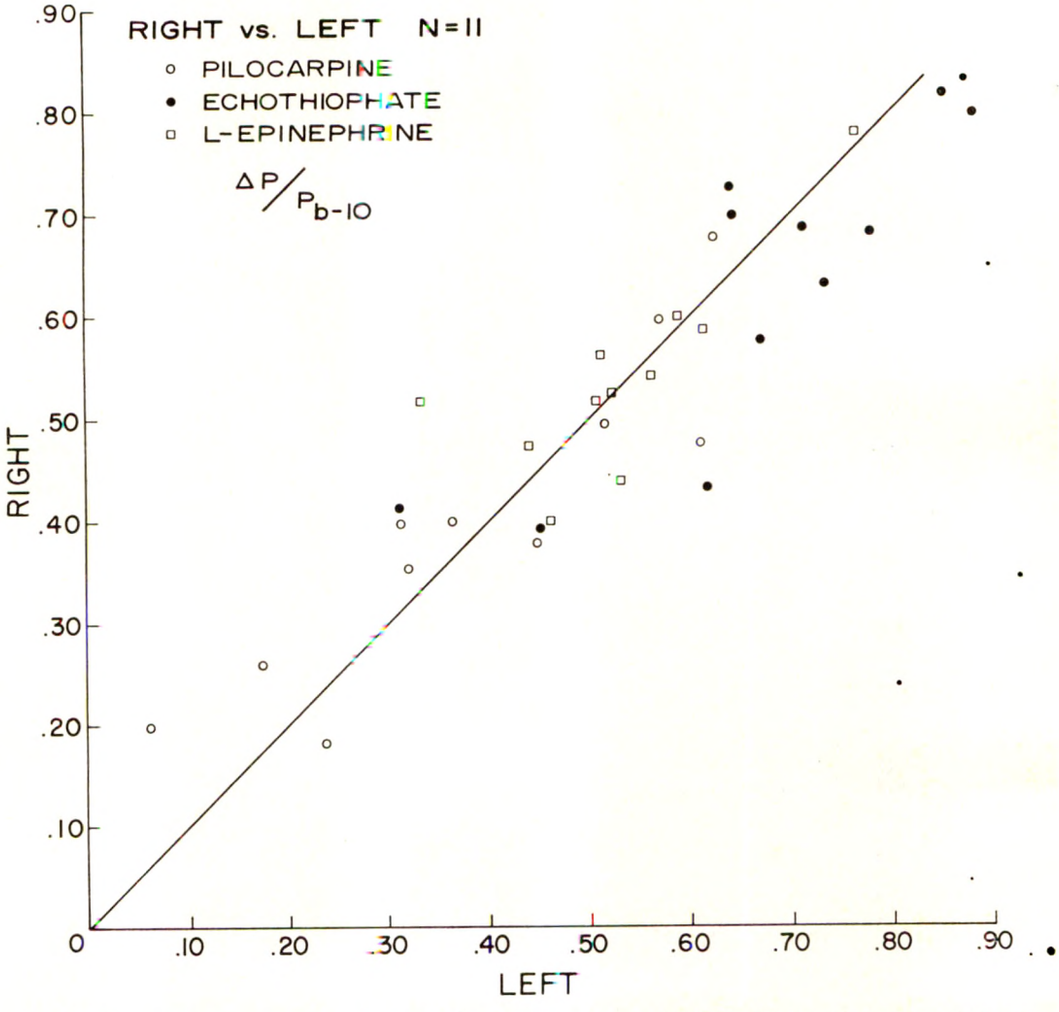



Fig. 7 (Kronfeld). The correlation between the pressure changes ($\Delta P/P_b$-10) in the right and left eye produced in patients with ocular hypertension or primary open-angle glaucoma (Series 6) by three-week courses of treatment with the agents indicated in the figure.

TABLE 8

FREQUENCY DISTRIBUTION OF THE EPINEPHRINE-INDUCED PERCENT OF INCREASE IN OUTFLOW FACILITY IN OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA

| Source of Data | Duration of Treatment | Percent Increase | | | | | | | | | Total No. Eyes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | −9 to 10 | 11 to 30 | 31 to 50 | 51 to 70 | 71 to 90 | 91 to 110 | 111 to 130 | 131 to 150 | 151 to 170 | |
| Present study (Series 6) | 3 weeks | — | — | — | 2 | 4 | 8 | 3 | 3 | 2 | 22 |
| Becker and associates[18] | 3 months | 9 | 7 | 10 | 4 | 3 | 1 | — | 2 | 1 | 37 |
| Becker and associates[19] | Up to 60 months | 4 | 15 | 12 | 9 | 6 | 1 | 3 | — | 1 | 50 |

phenomenon of relative tolerance that sets in after the first three weeks of treatment. A particularly pronounced form of this tolerance may have been the basis of the tachyphylaxis to the drug observed by Krill and Newell[22] in some of their cases. In the large majority of ocular hypertensive patients and those with primary open-angle glaucoma, a certain—and clinically very useful—measure of responsiveness is retained and becomes, in some cases, the starting level for the gradual gain in facility reported to occur on prolonged L-epinephrine therapy.[19,23]

### COMPARISON WITH OTHER HYPOTENSIVE DRUGS

Further characterization of L-epinephrine as a hypotensive agent was expected to derive from comparison of its effect with that of other drugs. The similarity between the effects of epinephrine and echothiophate, as shown in Figures 3 and 4, was closer than expected. In the evaluation of this similarity, allowance should be made for a possible lowering of ocular rigidity by echothiophate. The pressure drops shown in Figure 3 may, therefore, represent slight overstatements and the resistance drops of Figure 4 may be understatements of the actual changes that occurred in response to echothiophate.

Also, the dosages in which the two drugs were used may not have been equally close to the maximum effective dose for all the eyes included in the study. Echothiophate in 0.25% concentration once a day may represent less than the maximum dose, while 2% L-epinephrine twice a day is well in excess of the full dose. Still, in a qualitative and semi-quantitative sense the comparison of the two drugs is probably valid; it again brings out the strength and duration of the outflow-enhancing component in the effect of L-epinephrine. The responses of the individual eyes to the two drugs tend to be close together, suggesting essentially the same degree of responsiveness to both drugs. This probably applies only to eyes with base line pressures within the range represented in this study; in eyes with base line pressures in excess of 35 mm Hg the responses to echothiophate are generally distinctly better than the responses to topical L-epinephrine. This characteristic of the drug, however, does not apply to the massive doses delivered to the eye by subconjunctival injection of 0.1% solutions.

Comparison of the effects of L-epinephrine with those of pilocarpine are valid with regard to dosage; tonography performed four hours after the early morning administration indicated that in none of the patients of Series 6 could the effect of pilocarpine

4% be augmented significantly by 50% increase in dosage. A difference in effective dosage may have been introduced by the fact that most of the patients of Series 6 had been on sustained pilocarpine therapy prior to the study.

The comparison brings out well-known characteristics of pilocarpine—that is, marked individual variations in effect, smaller responses in general and, specifically, very small responses in the range of low base line pressures, a range in which L-epinephrine is conspicuously effective.

## Summary

The early effects of topical L-epinephrine on aqueous dynamics in primary ocular hypertension and primary open-angle glaucoma were studied with single doses and three-week courses of sustained administration. Several phases of the effect of the drug could be recognized, with increases in outflow facility emerging as the dominant response of the type eye under study. During the first three weeks of treatment the magnitude of the facility response was close to that of echothiophate, with suppression of aqueous production making a recognizable contribution to the lowering of intraocular pressure in only one-third of the eyes participating in the study.

The high level of facility response evidenced during the first three weeks of treatment is probably not uniformly maintained as treatment is continued.

### Acknowledgments

The technical assistance of Miss Joan Anderson and Mrs. Dora Hess is gratefully acknowledged.

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# RESULTS OF DEPRESSION BIOMICROSCOPY OF THE POSTERIOR CHAMBER

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The posterior chamber of the human eye has a complicated shape (Fig. 1). Salzmann[1] distinguishes several parts.

The most posterior part (i.e., the slit-shaped orbicular space named after Garnier[2]) extends between the inner face of the pars plana and the orbicular portion of the anterior limiting membrane of the vitreous.

The second part, the system of ciliary valleys, borders on the orbicular space posteriorly. In the posterior pars plicata, the ciliary valleys form closed canals, as the vitreous is adherent to the tips of the ciliary processes. In the anterior pars plicata, by contrast, the ciliary valleys present as grooves opening into the circumlenticular space.

The circumlenticular space itself constitutes the third part of the posterior chamber. Its outer and inner borders are formed by the ciliary processes and the peripheral lenticular zone, while it is delineated anteriorly and posteriorly by the anterior limiting membrane of the vitreous and the anterior zonule fibers.

The extreme anterior part of the posterior chamber (i.e., the prelenticular and prezonular space) extends from the pupil to the iris root. It borders anteriorly on the iris and posteriorly on the lens as well as the anterior zonule fibers.

Biomicroscopy of the posterior chamber in non-aphakic eyes has so far been limited. The prezonular and the circumlenticular space can be examined with the slit lamp only under exceptional circumstances. Such examination is possible (1) if there is a colomba or a dialysis of the iris, or (2) if the pupil can be dilated to the extent of forming an iridolenticular cleft. In this case, the iris contracts into a narrow seam and loses its contact with the anterior lens surface.

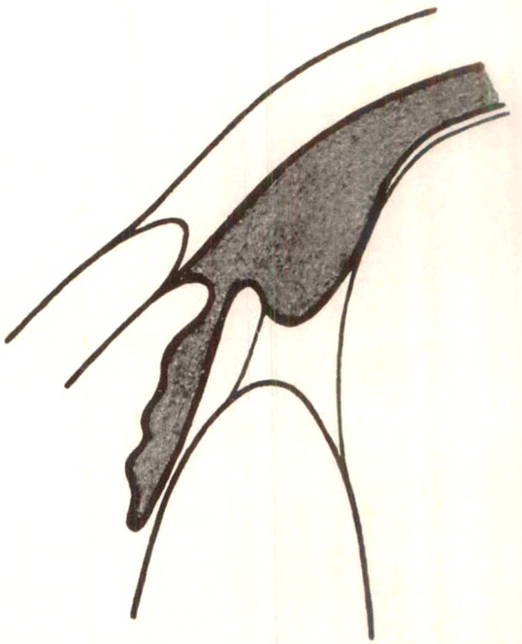


Fig. 1 (Slezak). Posterior chamber of the human eye.

The results obtainable on biomicroscopy of the posterior chamber through the iridolenticular cleft, using mirror contact lenses, are poor for two reasons: (1) The biomicroscopic visual field is narrow; hence, only a slit-shaped section of the posterior chamber can be viewed (Fig. 2). Further (2), the sections of the posterior chamber which are visible through the iridolenticular cleft are not magnified when contact lenses are used. Hence, details go unnoticed.

Visualization can be improved by depressing the sclera above the posterior chamber (Fig. 3). This ensures that the examination

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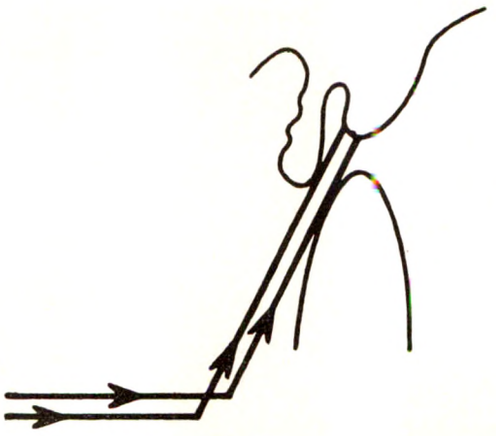


Fig. 2 (Slezak). Biomicroscopy of the posterior chamber through the iridolenticular cleft using a mirror contact glass.

can be done at a smaller angle of incidence, offering the following advantages:

1. The biomicroscopic visual field is considerably expanded, since the examination is no longer confined to the narrow space created by the iridolenticular cleft. Thus posterior chamber sections otherwise inaccessible to biomicroscopy become visible and can be observed with the slit lamp.

2. The size of the image is larger, as the posterior chamber is examined through the lens.

3. Though still necessary, dilatation of the pupil need not be extreme. Thus biomicroscopy of the posterior chamber is no longer confined to exceptional cases.

The auxiliary devices commonly used for slit lamp examinations of the ora serrata and the pars plana of the ciliary body[3-8] have no place in depression biomicroscopy of the posterior chamber, as the depression they make is not sufficiently anterior. These devices reach the orbicular space.

To visualize those parts of the posterior chamber anterior to the orbicular space along the translenticular route, I used a *funnel*, initially, with the three-mirror contact lens[9] (Fig. 4), the depressor of which partially overlapped with the scleral seam of the contact lens. Thus I succeeded in depressing the eyeball anterior to the anterior margin of the pars plana. As experience accumulated, I found that visualization of the posterior chamber is improved when the depressor completely rests on the scleral seam of the contact lens. This ensures that the iris-root recess of the prezonular space can also be observed with the slit lamp. Consequently, I have come to use a contact lens (Fig. 5) with a broad scleral seam, the mirror of which is

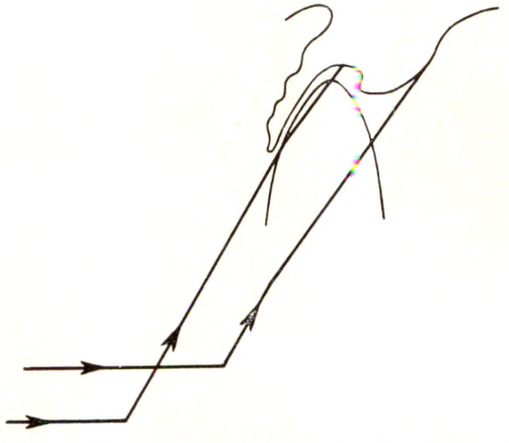


Fig. 3 (Slezak). Translenticular biomicroscopy of the posterior chamber after scleral depression.

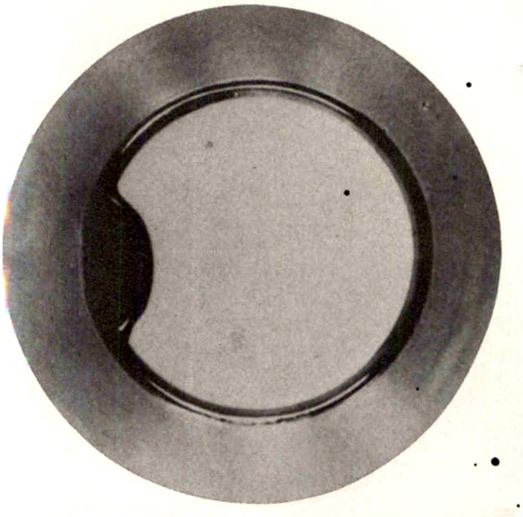


Fig. 4 (Slezak). Ciliary body depression funnel (for biomicroscopy of the pars plicata of the ciliary body).

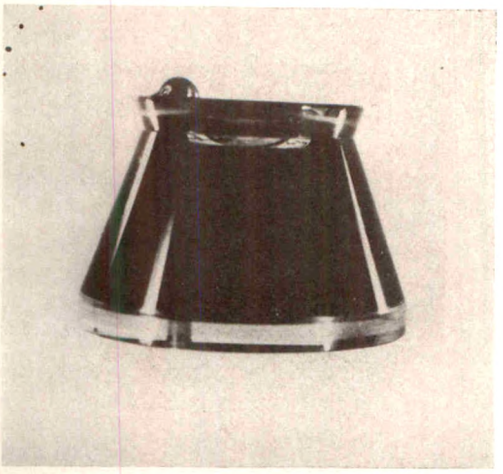


Fig. 5 (Slezak). Posterior chamber contact glass.

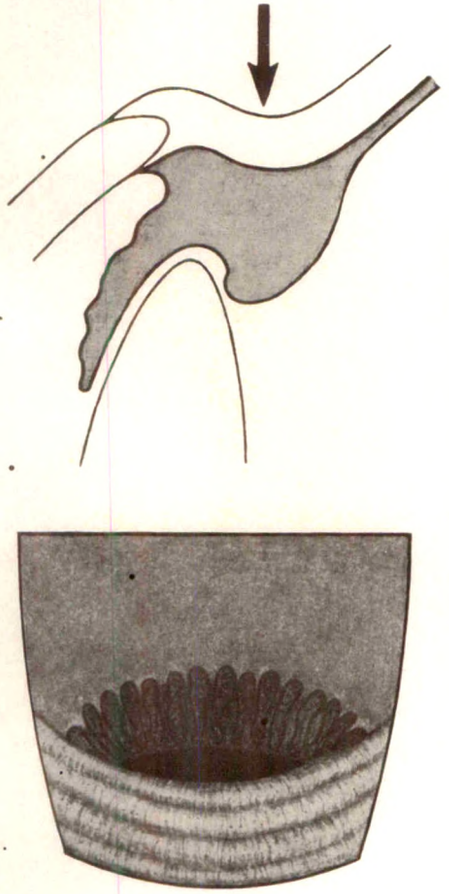


Fig. 6 (Slezak). Top: Scleral depression above the posterior chamber. Bottom: Mirror image of the depressed part of the posterior chamber.

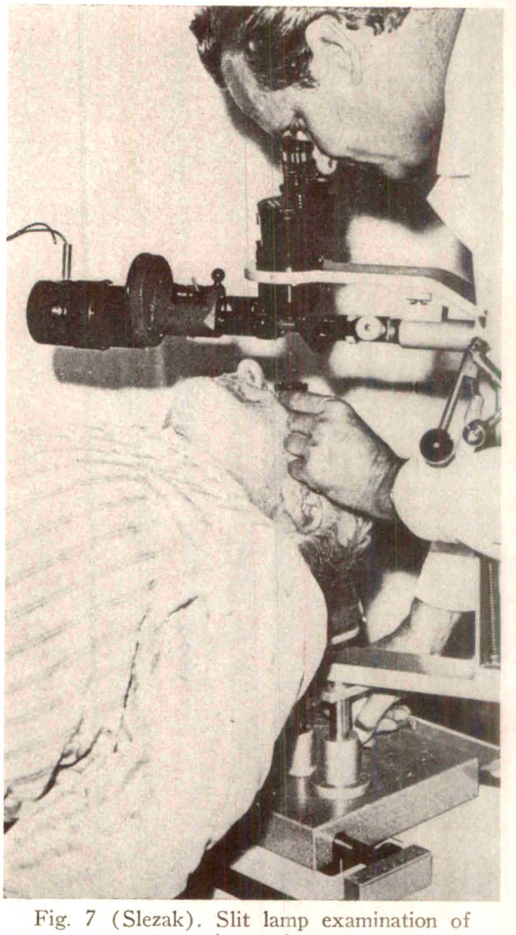


Fig. 7 (Slezak). Slit lamp examination of supine patient.

inclined 66 degrees to the anterior surface. Its spherical depressor is embedded in the scleral seam right next to the corneal excavation and impresses the eyeball above the posterior chamber. The depressed area then becomes visible in the mirror of the contact lens (Fig. 6). The pupil of the examined eye is also visualized, but its mirror image is deformed ovally. This oval deformation of the pupillary mirror image at times limits the usefulness of the binocular translenticular slit lamp examinations in the temporal and nasal sections of the posterior chamber. Whenever this occurs the patients are examined in the supine position, using a special version of the slit lamp which I developed in collaboration with Haag-Streit (Fig. 7). The

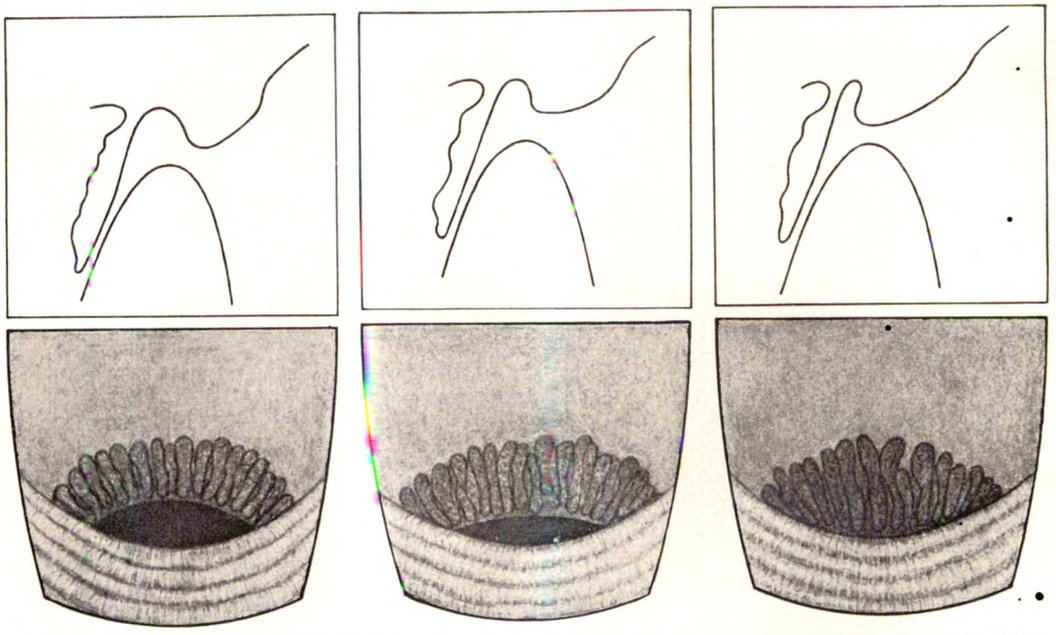
prototype is still subject to improvements and thus is not yet available on the market.

## Results and comments

Examination with the posterior chamber contact lens supplies information on the topographic relations between the anterior chamber angle and the iris root recess of the posterior chamber. The latter may be wide, of medium width, or narrow. If the recess is wide (Fig. 8), a wide brown area is seen in front of the tips of the ciliary processes. At medium width of the recess (Fig. 9), this area is rather small. It corresponds to the wall of the recess. If the recess is narrow (Fig. 10), its wall can no longer be seen. The image is confined to the anterior margin of the tips of the ciliary processes. The configuration of the iris root recess depends on the width of the anterior chamber angle and the length of the ciliary processes. If the anterior chamber angle is narrow, the recesses should be wide, and vice versa. Discrepancies between the findings of anterior and posterior gonioscopy serve as an indicator for the length of the ciliary processes. Small anterior chamber angles and narrow iris root recesses are associated with relatively long and overhanging ciliary processes, while large angles and wide recesses suggest short and flat processes.

As a rule, the wall of the iris root recess is smooth, but at times it presents a relief of radial ridges and bulges (Fig. 11). Occasionally, an abnormally long ciliary process reaches into the iris root recess.

The posterior chamber contact lens is extremely useful in examining eyes with vitreous opacities of unknown etiology. Recently, I examined a patient with recurring vitreous opacities involving the right eye. Both the choroid and the pars plana of the ciliary body were free from inflammatory lesions. The retinal vessels were also normal. Hence, I initially suspected a serous posterior cyclitis, but depression biomicroscopy of the posterior chamber lead to the right diagnosis: Several tips of ciliary processes inferotem-



Figs. 8-10 (Slezak). Left: Wide iris root recess. Overview (top) and mirror image after scleral depression (bottom). Center: Iris root recess of medium width. Overview (top) and mirror image after scleral depression (bottom). Right: Narrow iris root recess. Overview (top) and mirror image after scleral depression (bottom).

porally had fused into a grayish-yellow nodule (Fig. 12). This suggested a granulomatous anterior cyclitis. About 10 minutes after the intravenous injection of fluorescein the nodule had a patchy green appearance. Shortly afterward, the stain leaked into the vitreous. The nodule was therefore the cause for the recurring vitreous opacities.

I am not aware of any reports on the condition of the posterior chamber in cases of rubeosis iridis. Therefore, I examined patients with this disease at the slit lamp, using the posterior chamber contact lens. Since vascularized tissue is often found in the anterior chamber angle in this condition, I suspected similar changes to be present in the posterior chamber, but, with one single exception, this assumption proved wrong. In all such eyes examined, both the ciliary processes and the iris root recesses were normal, except for one case in which an island of vascularized tissue was seen in the iris root recess (Fig. 13). Further studies will prove whether this finding is more common than our experience seems to suggest.

Conceivably, the posterior chamber contact lens may also be useful for photocoagulation. The technique of photocoagulation as described by Fankhauser and Lotmar[10] has thus far been confined to the peripheral retinal region and pars plana. With the help of the posterior chamber contact lens it can be extended to the pars plicata of the ciliary body. Photocoagulation of the ciliary processes may be tried whenever an operation is indicated in glaucomatous aphakic eyes.

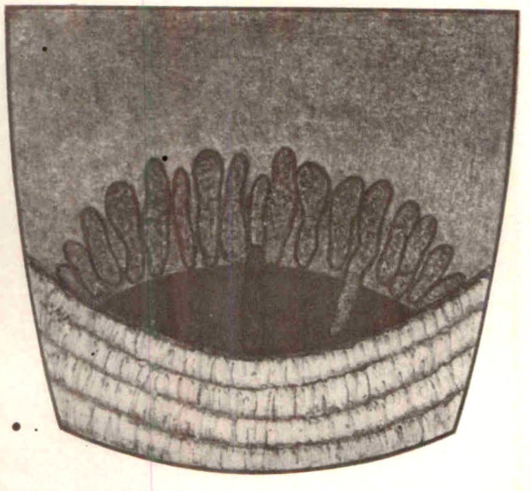


Fig. 11 (Slezak). Wall of the iris root recess with thin radial ridge, radial bulge and abnormally long ciliary process.

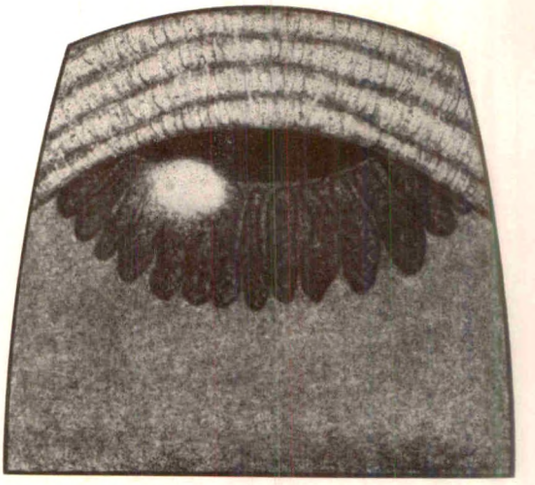


Fig. 12 (Slezak). Granulomatous inflammatory focus in the area of the tips of the ciliary processes.

The posterior chamber in nonaphakic eyes was previously accessible to biomicroscopy only in exceptional cases. Now slit-lamp examination of the posterior chamber is almost always successful.

## Summary

With the help of a depression contact lens, the posterior chamber can now be examined

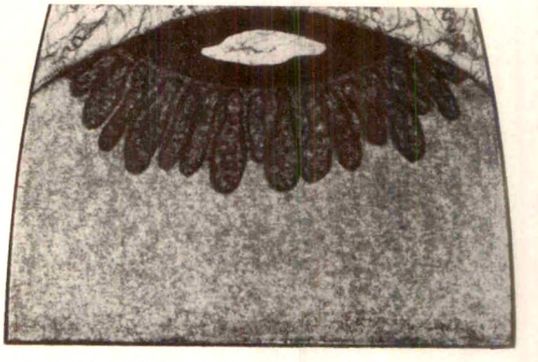


Fig. 13 (Slezak). Vascularized tissue in the iris root recess.

by slit lamp along the translenticular route, even without maximal pupillary dilation. This posterior chamber contact glass for the posterior gonioscopy has a mirror that is inclined 66 degrees to the anterior surface. Its spherical depressor is embedded in the scleral seam right next to the corneal excavation and impresses the eyeball above the posterior chamber. The depressed area then becomes visible in the mirror of the contact lens. Photocoagulation of the ciliary processes through the posterior chamber contact glass can be performed in glaucomatous aphakic eyes.

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## Ophthalmic Miniature




The eye of Horus.

# AGING CHANGES OF THE CILIARY EPITHELIUM BORDER LAYERS AND THEIR SIGNIFICANCE FOR INTRAOCULAR PRESSURE

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With advancing age, alterations in the trabecular meshwork of human eyes include hyalinization,[1] proliferation of long-spacing collagen,[2] and reduction in the number and size of the vacuolated cells in the endothelial lining of the trabecular wall.[3] These alterations are thought to lead to an increase in the resistance to aqueous outflow. However, in aging persons whose eyes are healthy, pressures are not much higher pressures than the norm for younger eyes.[4] Thus, it seems reasonable to conclude that in spite of the increase in the resistance to outflow, intraocular pressure is maintained at about the same level during life by a progressive decline in aqueous secretion.[5]

The present paper deals with some fine structural properties of the external and internal surface of the ciliary epithelium of the human eye. Our observations suggest that aging changes of the extracellular limiting layers of these surfaces, especially at the internal surface of the nonpigmented ciliary epithelium, may be due to a progressive diminution in the rate of formation of the aqueous humor. The fine structural alterations are already present in young adult eyes and these proceed in the later decades of life.

## MATERIALS AND METHODS

Materials were obtained from eyes which were surgically removed from patients aged nine months, 29, 31, 34, 58, 61, 77, and 78 years with retinal or uveal tumor. In all cases, the tumor was situated at the posterior pole or opposite the excised tissue. The appearance of the disk clinically and histologically was normal. In one case (the nine-month-old child), ocular tension was not measured. The intraocular pressure of the other eyes used for this investigation ranged between 14 and 19 mm Hg.

The specimens to be studied by electron microscopy were prepared in the same way as described in previous papers[6,7] and examined in a Zeiss EM 9-A or EM 9-S electron microscope.

## OBSERVATIONS

In early childhood there is no fundamental difference between the basement membranes (basal lamellae) of the ciliary capillaries and those on the outer (base of the pigment epithelium) and inner (area lining the posterior chamber) surface of the ciliary epithelium. Furthermore, there is no difference between these ciliary basement membranes and the basement membranes covering the outer and inner surface of the neural retina, i.e., posterior to the ora serrata.

Both in the pars plana and in the pars plicata, the basement membranes of the capillaries and of the pigmented and nonpigmented ciliary epithelium consist of only one sheet, a lamina densa of the usual appearance. From the adjacent cells it is mostly separated by a light zone up to 50 nm wide (lamina rara). Occasionally, no lamina rara exists and the lamina densa immediately

ABBREVIATIONS IN FIGURES 1–9

| | |
|---|---|
| BM | Basement membrane (basal lamella, basement membrane material) |
| C | Collagen |
| CL | Capillary lumen |
| D | Desmosome |
| EL | Elastic fiber |
| END | Endothelial cell |
| F | Fibroblast (fibrocyte) |
| IS | Intercellular space |
| NPE | Nonpigmented epithelium |
| PE | Pigment epithelium |
| Z | Zonular fibril bundle |

From the ophthalmological clinic of the university of Mainz. This study was supported by the Deutsche Forschungsgemeinschaft.

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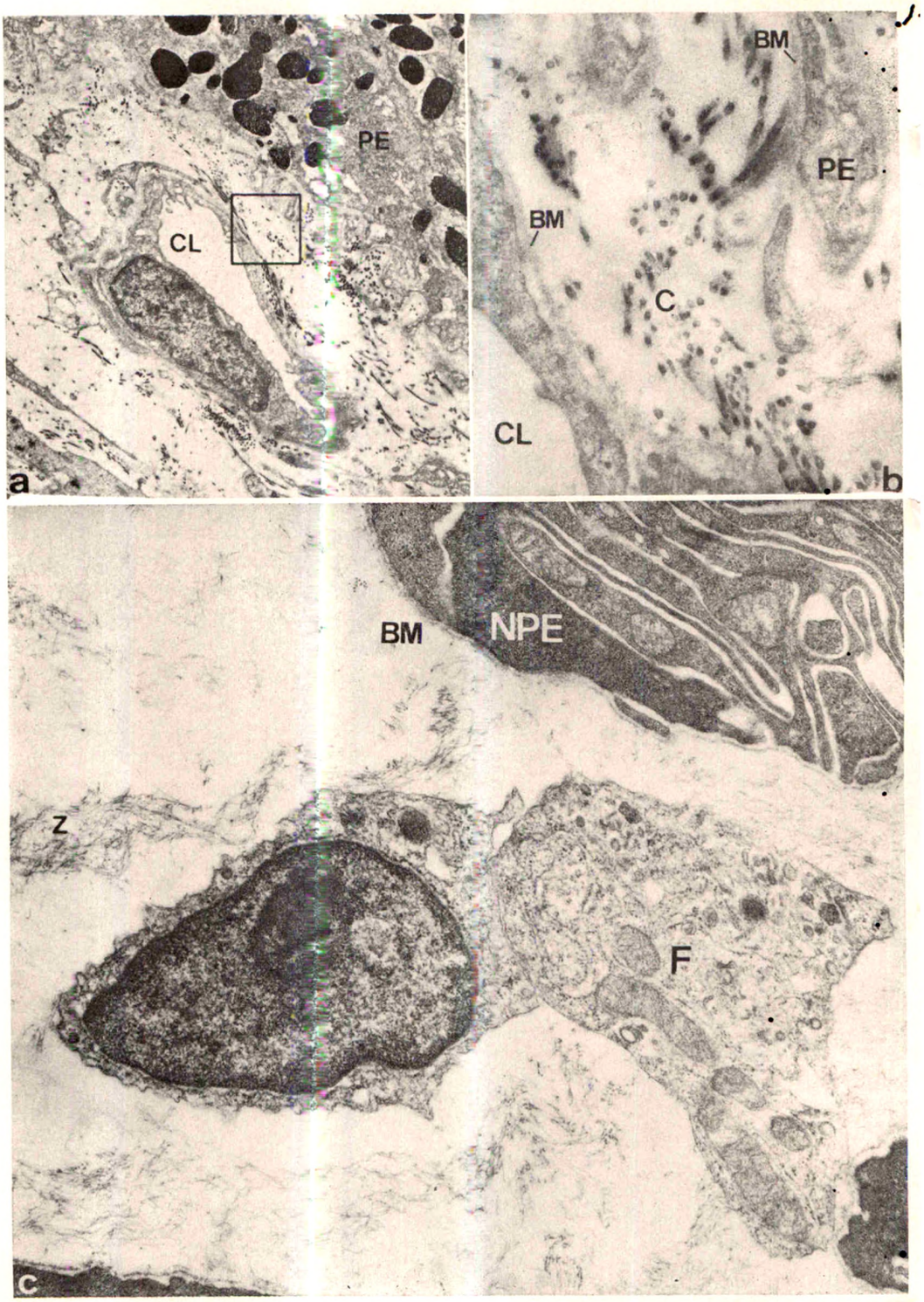



Fig. 1 (Gärtner). Girl, aged nine months. Pars plicata. (a) External surface of the ciliary epithelium. Perivascular extracellular space around a capillary (×5000). (b) Area boxed in a, other plane of section (×23,000). (c) Internal surface. The basement membrane is single-layered, as on the external surface and on the capillary wall (uranyl acetate-permanganate, ×21,000).

follows the contour of the adjacent cell membrane.

At the capillary wall, and at the outer surface of the ciliary epithelium, the average thickness of the lamina densa is 55 nm. At the inner surface of the ciliary epithelium the basement membrane seems to be thinner. The average thickness is 33 nm, both in the pars plicata (Fig. 1) and in the pars plana (Fig. 2).

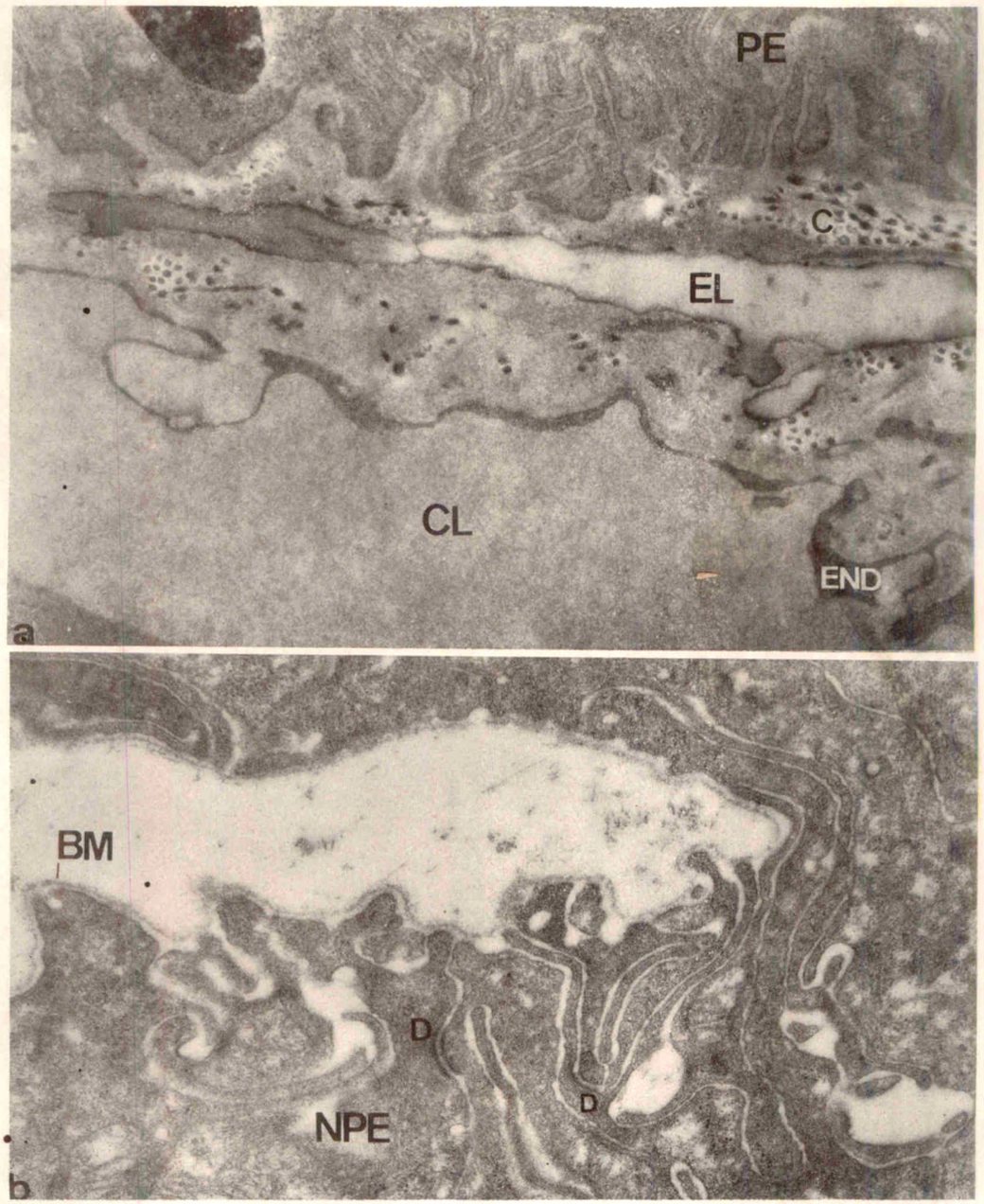



Fig. 2 (Gärtner). Girl, aged nine months. Pars plana. (a) External surface of the ciliary epithelium. Perivascular extracellular space between a capillary and the pigment epithelium, filled with a homogeneous substance (×23,000). (b) Internal surface. The basement membrane is single-layered.

In many areas between the capillary wall and the pigment epithelium it is impossible to demarcate the laminae densae adjacent the capillary wall and the pigment epithelium from the mean rest of "unformed" contents of the perivascular extracellular space. These contents are a lightly staining, homogeneous, fine granular or filamentous substance, which encloses collagen fibrils, cellular components, and occasionally elastic fibers. The described substance has a very similar aspect to the fluid portion of blood within the capillary lumina. It may be present both in the pars plicata and in the pars plana (Fig. 2).

In the adult eye, the perivascular extracellular space between the capillary wall and the pigment epithelium widens considerably. The lightly staining homogeneous substance may reach a thickness of several microns (Fig. 3-A). Also the basement membrane material at the inner surface of the ciliary epithelium has a very different appearance from that in early childhood. It forms a marked network, especially in the pars plicata, but also within the bays of the pars plana. As already described in previous papers,[6,8] most of the meshes of this network are occupied by osmiophilic granular and lamellar deposits, probably lipid-containing substances (Figs. 3-B and 4). At higher magnifications, the deposits show a fine parallel striation that consists of alternating light and dense lines. The periodicity of the striation varies about a mean value of 3.4 nm. Like the homogeneous substance in the extracellular space between the ciliary capillaries and the pigment epithelium, the basement membrane network already in young adult eyes may reach a thickness of several microns.

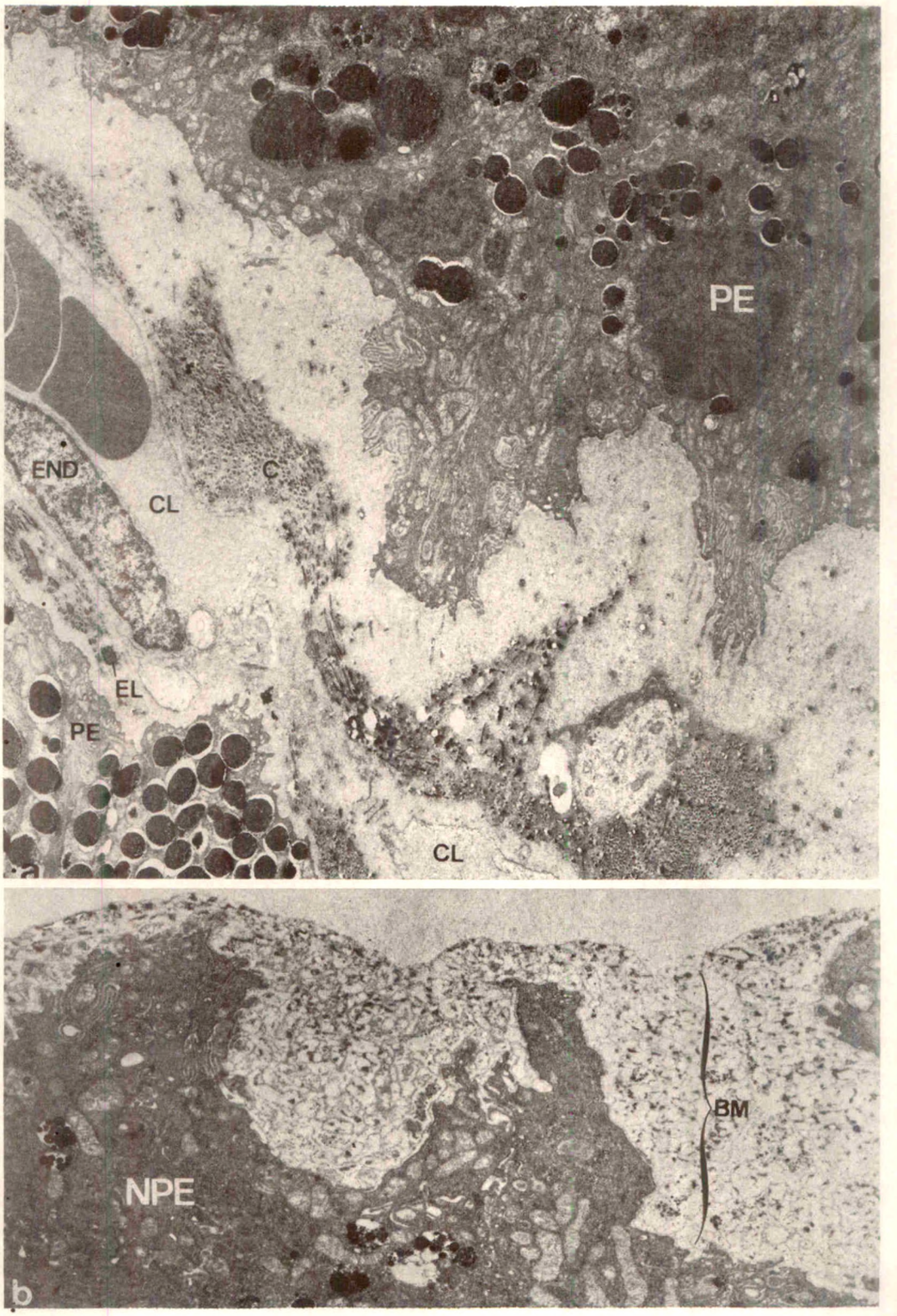
In the cytoplasm of the nonpigmented ciliary epithelium vacuoles and lipid-containing granules of different size occur.

Unlike the basement membrane network at the inner surface of the ciliary epithelium, the perivascular extracellular space between the ciliary capillaries and the pigment epithelium usually does not contain granular or lamellar accumulations of the described type. At higher resolution, this space has a fine granular or filamentous appearance; it is exactly like the common basement membrane material. On the other hand, it is hardly distinguishable from the fluid contents of a capillary lumen, filled with plasma proteins (Fig. 5).

With increasing age the basement membrane network at the inside of the ciliary epithelium becomes thicker. In an eye that was 73 years of age, it measured twice the thickness than in eyes that were 29 and 34 years old. The meshes of the network contain much more granular and lamellar deposits than can be found in young adult eyes. Also, the perivascular extracellular space between the ciliary capillaries and the pigment epithelium further increases in thickness. Osmiophilic granular and lamellar deposits either lack or are visible only at a very few places within this space (Figs. 6 and 7).

The cytoplasm of the nonpigmented ciliary epithelium of senile eyes shows marked changes from that observed in young adult eyes. They are due to an increase in the number and size of intracytoplasmic vacuoles and especially to an enormous increase in the number of the lipid-containing compound granules (Figs. 7 and 8). These granules may be membrane-bounded, but some differ from the others in their lack of an encirculing membrane. Their dense contents

Fig. 3 (Gärtner). Woman, aged 31 years. Pars plicata. (a) External surface of the ciliary epithelium. Perivascular extracellular space around two capillaries, filled with a homogeneous substance (×5000). (b) Internal surface. Basement membrane network, filled with lipid deposits. Pigment granules, most probably lipofuscins, in the nonpigmented epithelium (uranyl acetate-permanganate, ×5000).


PE
END
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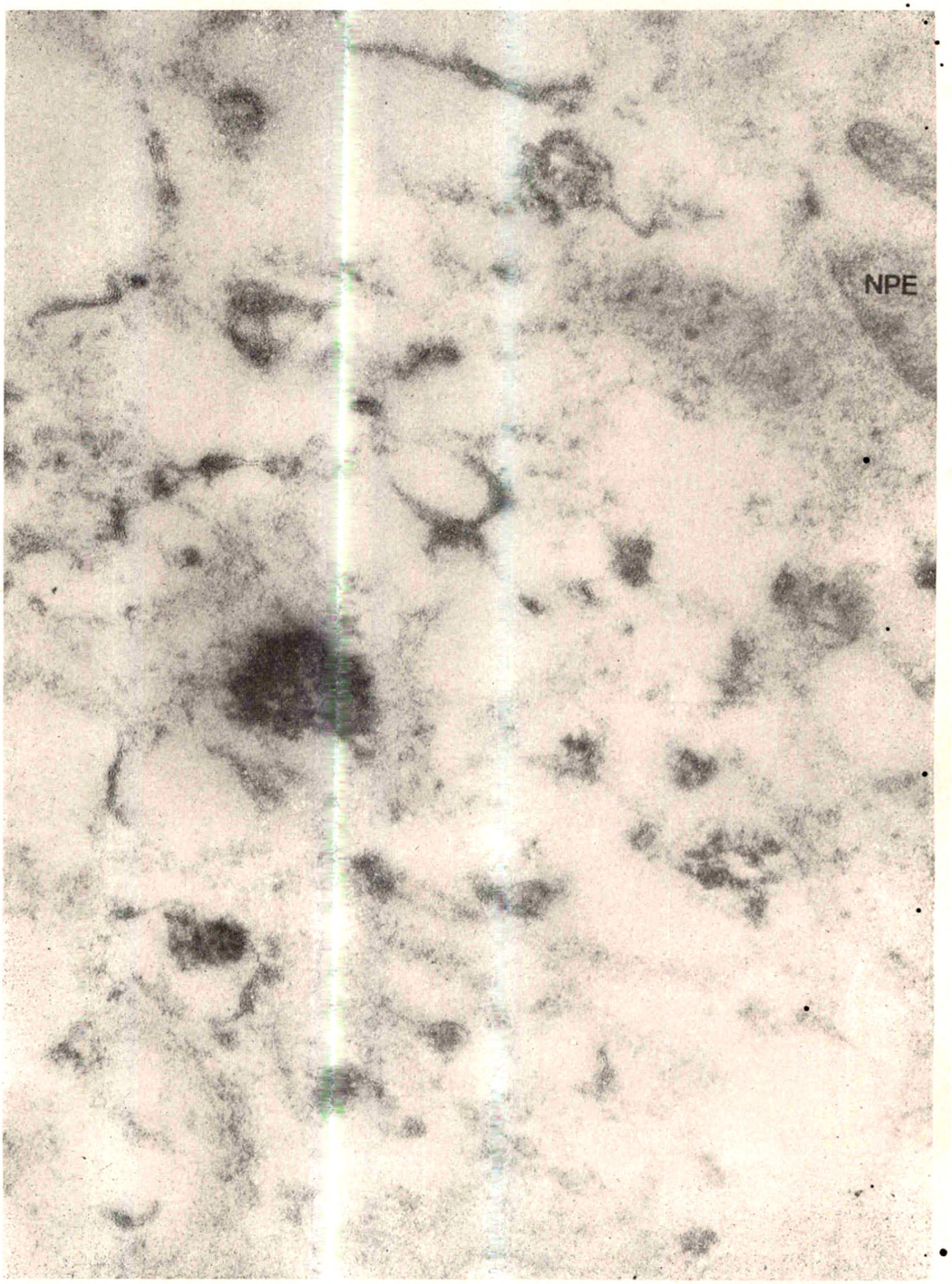



Fig. 4 (Gärtner). Woman, aged 29 years. Internal surface of the ciliary epithelium. Lipid deposits within the meshes of the basement membrane network (uranyl acetate-permanganate, ×80,000).

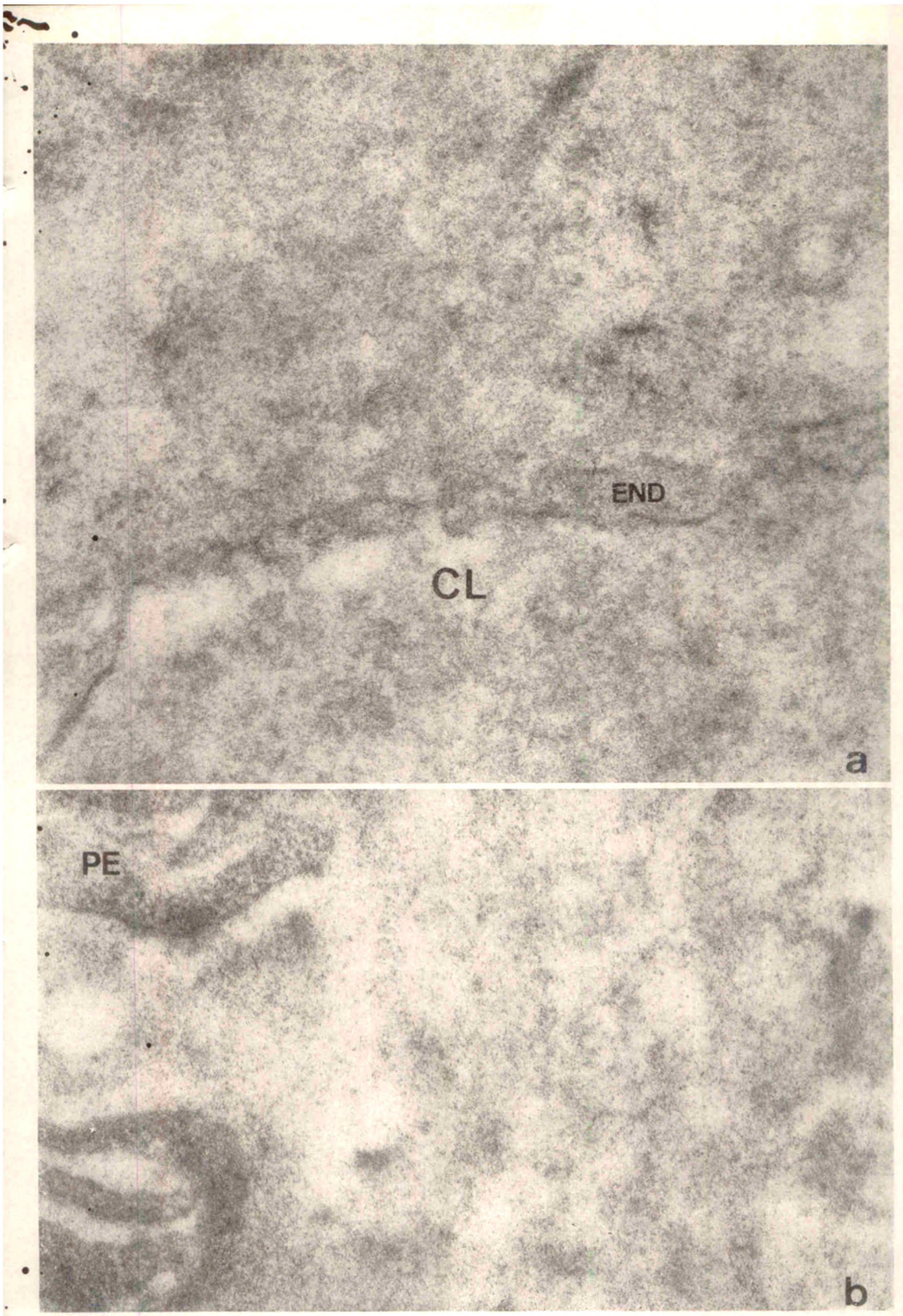



Fig. 5 (Gärtner). Woman, aged 31 years. Pars plicata. External surface of the ciliary epithelium. (a) Capillary lumen and perivascular extracellular space, showing a fine granular substance in this higher magnification (×80,000). (b) Perivascular extracellular space and pigment epithelium. Poorly defined meshes of basement membrane material, filled with the same fine granular material (uranyl acetate-permanganate, ×80,000).

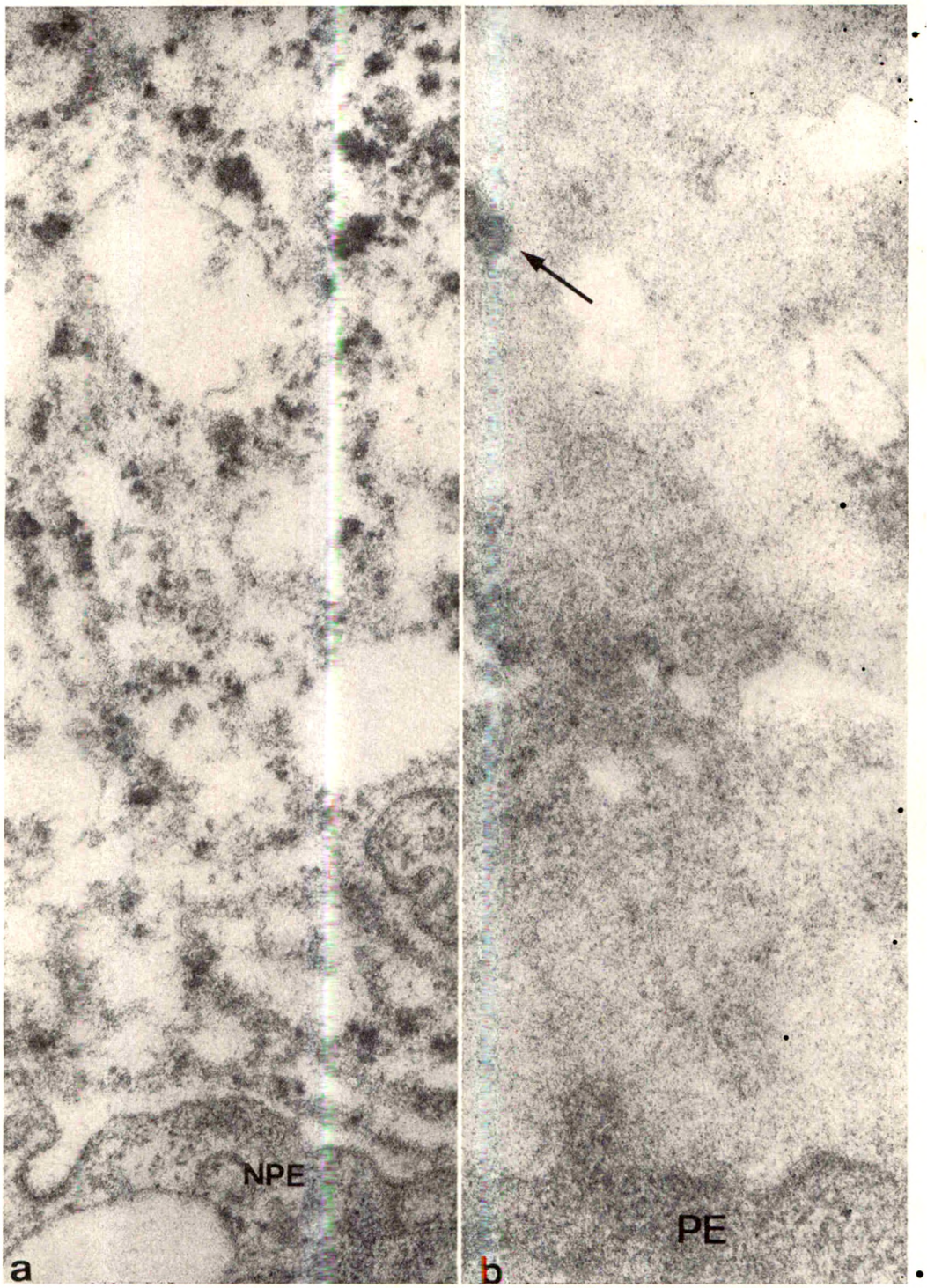



Fig. 6 (Gärtner). (a) Man, aged 61 years. Pars plicata. Internal surface of the ciliary epithelium. Basement membrane network, filled with lipid deposits (×80,000). (b) Woman, aged 78 years. Pars plicata. External surface. Fine granular substance in the perivascular extracellular space between the pigment epithelium and the ciliary capillaries. Lipid deposit can be seen at only one place (arrow) (uranyl acetate-permanganate, ×80,000).

are formed of round, sometimes dust-like particles, and of lamellae which may be arranged in form of myelin figures. Most of the otherwise dense compound granules contain vacuoles of low density. These are of different size, and usually placed in the periphery. Within the dilated intercellular spaces near the inner surface of the nonpigmented epithelium myelin figures were observed, which may be fragments of the compound granules (Fig. 8).

Osmiophilic granular and lamellar material is also present within degenerating or necrotic cells outside the ciliary epithelium; apparently fibroblasts of the zonular apparatus. These cells occur in various stages of disintegration, sometimes immediately adjacent to the basement membrane network at the inner surface of the ciliary epithelium (Fig. 9).

## Discussion

The sponge-like structure of the basement membrane at the internal surface of the ciliary epithelium is a usual finding in adult human[5,8,9,10,11] and in bovine[12] eyes. In the early stages of life it could not be observed, at least not in our material. There is a distinct accentuation of this structure in advanced age. We believe that the transformation of the originally single-layered basement membrane into a multilayered network is mainly caused by biomechanical forces exerted by the adhering zonular fibers.[8,13] The common aging processes, leading in most tissues to a well-known augmentation of basement membrane material, may be an additional factor.

The external surface of the ciliary epithelium of the adult human eye is completely different from the internal surface. At the external surface no sponge-like basement membrane is visible, but only a rather homogeneous substance in the perivascular extracellular space between the capillary wall and the pigment epithelium. Like the basement membrane network at the internal surface, the homogeneous substance may reach a thickness of several microns with advancing age. At most places it is not possible to recognize a distinct demarcation between this substance and the sheets of basement membrane material adjacent to the endothelial cells, the pigment epithelium, or protruding into the perivascular extracellular space between them. On the other hand, both in the perivascular extracellular space and in the capillary lumina, the same fine granular material may be observed. It must be called to mind that the endothelial cells of the ciliary capillaries are fenestrated like the endothelia of the plexus chorioideus,[14] the choriocapillaris,[15,16] the glomerulum,[17] the sinusoides of the liver,[18] and of other areas with increased transport functions. On the basis of these fine structural conditions, the perivascular extracellular space between the ciliary capillaries and the pigment epithelium may be regarded as a part of the blood space, as it is proposed also for Disse's space in the liver,[18] (e.g., as in Disse's space, the abundance of a homogeneous fine granular material in the extracellular space between ciliary capillaries and pigment epithelium could be the result of a more solid condition of aggregation of the substances passing this space during the processes of metabolism and aqueous humor formation). Our electron microscopic findings suggest that these substances might be plasma proteins.

Experiments with $^{131}$I-labeled albumin, which were performed to study the protein exchange in the eye, have shown that in the ciliary processes the perivascular albumin space is much larger than in the rest of the anterior uvea and that the main blood aqueous barrier to proteins is not located in the capillary walls. As only 10% of the albumin that leaves the vessels appears in the aqueous humor, it is assumed that the rest has to be metabolized, return into the vessels, or pass out of the eye by other routes.[19] Thus, it seems reasonable to conclude that the gel-like structure visible by electron microscopy in the extracellular space between the ciliary capillaries and the pigment epithelium, usu-

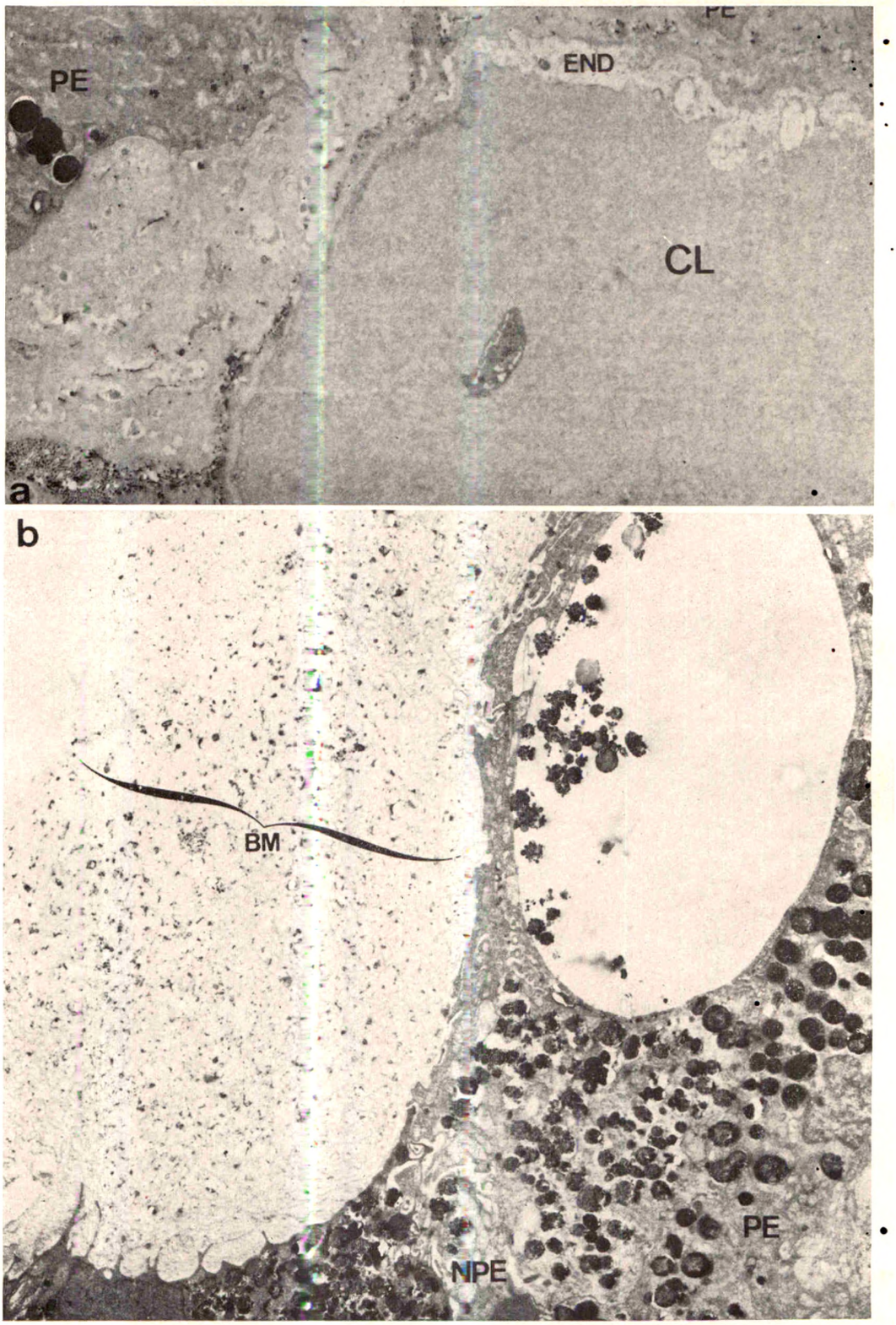



Fig. 7 (Gärtner). Woman, aged 78 years. Pars plicata. (a) External surface of the ciliary epithelium. Perivascular extracellular space, filled with a homogeneous substance, which is also visible in the large

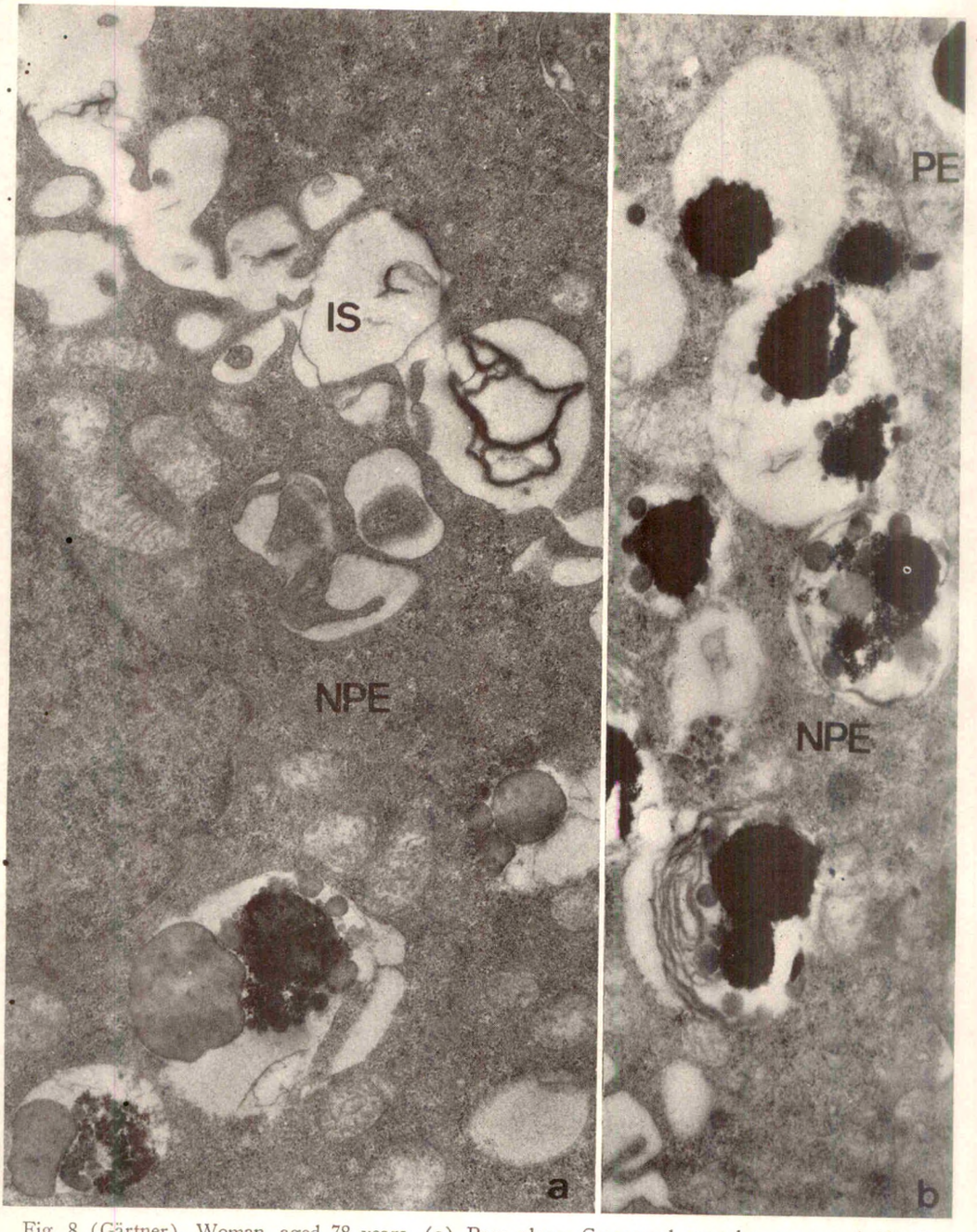



Fig. 8 (Gärtner). Woman, aged 78 years. (a) Pars plana. Compound granules, most probably lipofuscins, in the cytoplasm of the nonpigmented epithelium cells. Myelin debris in a widened intercellular space, which communicates with the meshes of the basement membrane network at the internal surface (×23,000). (b) Pars plicata. Compound granules, most probably lipofuscins, in the border areas between pigmented and nonpigmented ciliary epithelium (uranyl acetate-permanganate, ×23,000).

capillary lumen (×5000). (b) Internal surface. Lipid deposits within the meshes of the basement membrane network. Numerous compound granules, most probably lipofuscins, within the cytoplasm of the nonpigmented epithelium. Also the large vacuole in the nonpigmented epithelial cell represents aging effects (uranyl acetate-permanganate, ×5000).

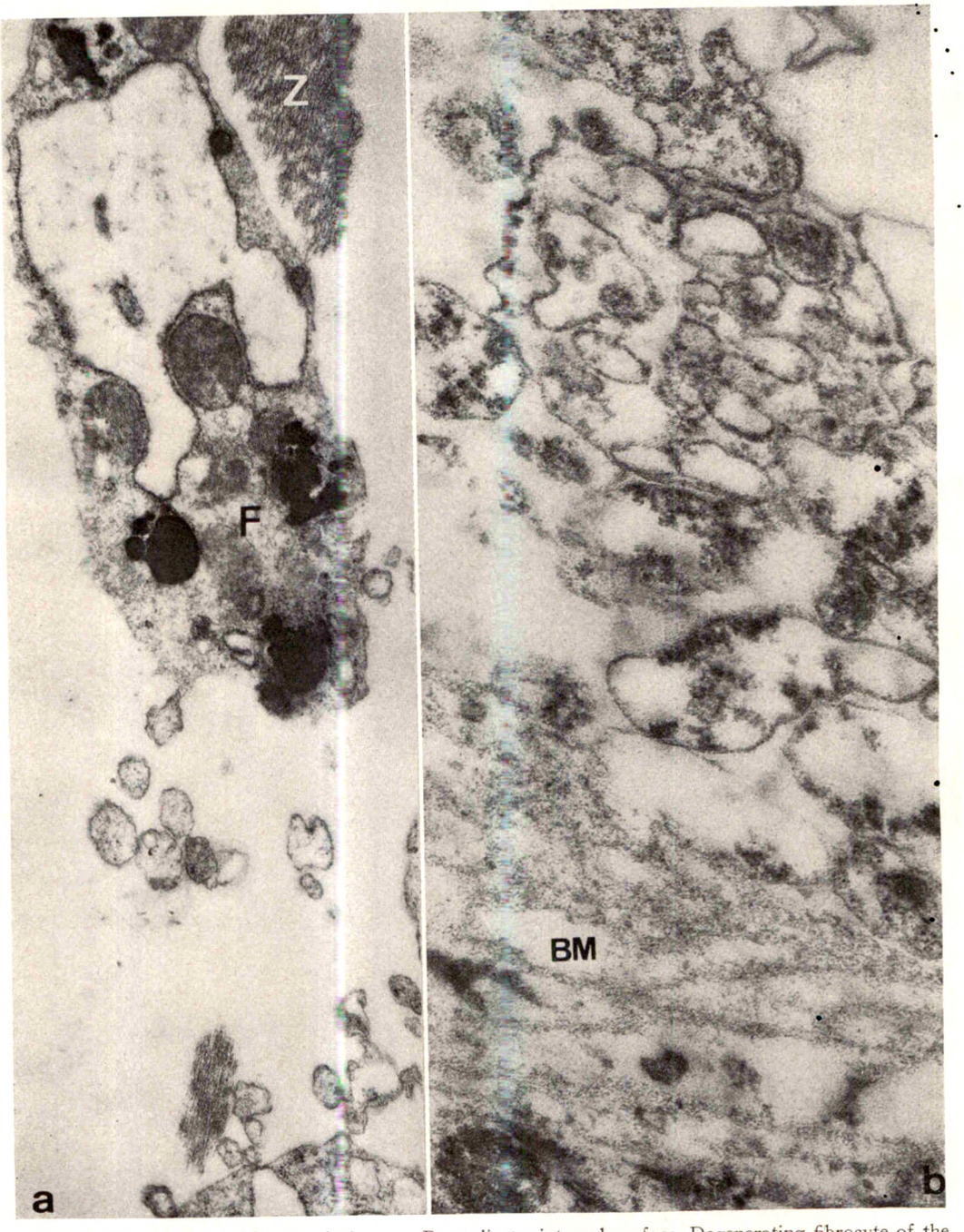



Fig. 9 (Gärtner). (a) Man, aged 61 years. Pars plicata, internal surface. Degenerating fibrocyte of the zonular apparatus. Note the abnormally dilated cisterna of the rough endoplasmic reticulum and the electron-dense lipid droplets (×21,000). (b) Woman, aged 78 years, Pars plicata, internal surface. Cellular detritus, most probably originating from a necrotic fibrocyte, adjacent to the basement membrane network (uranyl acetate-permanganate, ×21,000).

ally designated as thickened basement membrane, is not exclusively the basement membrane material pre-existing and augmented here, but also a variable symptom of aqueous secretion. The amount, the composition, and the condition of aggregation of all the contents of this space must be influenced by the protein concentration between capillary wall and pigment epithelium—that is, by the actual transport of water from this space into the ciliary epithelium. This could explain the changing fine structural aspects of the space —sometimes "empty," but mostly filled with the described gel-like structure.

It is a very interesting finding that in the extracellular space between the ciliary capillaries and the pigment epithelium practically no lipid-containing deposits are present. This is a marked difference from the basement membrane network at the inside of the ciliary epithelium, which is packed with such deposits, especially in senile eyes. With regard to this localization of the deposits, one might suggest that they originate from the compound granules within the nonpigmented ciliary epithelium. Fragments of these granules could be pushed out through the widened intercellular spaces together with the fluid of aqueous and trapped within the meshes of the network. As to the nature of the compound granules, it seems likely that they are lipofuscins according to the description of these elements given for the nervous system,[20] the retina,[21] and other tissues.[22] Lipofuscin granules constitute a type of residual body. They are now generally considered to be a form of lysosomes.[23] As the localization of acid phosphatase is the most important identifying characteristic of these particles, it must be stressed that the nonpigmented ciliary epithelium contains much acid phosphatase activity.[24,25] There might be some connection between lysosomes and melanin. The presence of acid phosphatase recently was demonstrated in neuromelanin granules, and electron microscopy reveals what appears to be lipid globules in neuronal melanin. It seems that lipofuscin and neuronal melanin are not as distinct as thought previously.[26] Furthermore, the possibility that some of the compound granules might be phagocytosed or even synthesized[8] melanin granules, cannot absolutely be ruled out.

The deposits could also originate in a second way, namely by the detachment of distal parts of nonpigmented epithelium cell processes or from disintegration of degenerating fibrocytes of the zonule. An analogous mechanism is believed to be responsible for the deposition of lipid debris within the aged cartilage matrix, which undoubtedly originate from necrotic chondrocytes.[27] Finally, the deposits may be the result of a biochemical disturbance leading to changes in the basement membrane synthesis.[8] It is well known that normal basement membrane material contains lipid substances. In the isolated basement membranes of the renal cortex of the rat, for example, 16.9% total lipids were found.[28]

Whatever explanation might be the most probable, our findings suggest the possibility that outflow facility from the ciliary epithelium into the posterior chamber may be decreased by changes occurring at the internal surface with advancing age. These changes are thickening of the basement membrane material as a whole, and interposition of lipid deposits within the meshes of its unique network. It seems obvious that especially the age-dependent interposition of lipids may influence the permeability of the basement membrane barrier at the ciliozonular border area, both in the pars plicata and in the pars plana. At the external surface also, a thickening of the homogeneous substance in the perivascular extracellular space between the ciliary capillaries and the pigment epithelium is observed with increasing age. However, even in senile eyes, we could not find in this substance the amount of lipid deposits occurring in the basement membrane network at the internal surface of the ciliary epithelium. In our opinion, there seems to be little doubt that the decrease in outflow in Schlemm's channel with advancing age is compensated

by a lower aqueous secretion caused by an increase in the resistance to aqueous outflow from the nonpigmented ciliary epithelium.

## Summary

In an electron microscopic examination of the fine structure of the ciliary epithelium of the human eye, mainly basement membranes, the changes that are observed are attributed to aging. With advancing age, the cytoplasm of the nonpigmented ciliary epithelium contains vacuoles and numerous compound granules, probably lipofuscins. The basement membrane at the inner surface is single-layered in early childhood, whereas in the adult eye it forms a multilayered network. At the external surface of the ciliary epithelium, a rather homogeneous substance in the perivascular extracellular space between the ciliary capillaries and the pigment epithelium is visible. This substance is considered not exclusively as basement membrane material, but also as a gel condition of plasma proteins leaving the capillaries. The basement membrane network at the internal surface contains lipid deposits which are not observed within the homogeneous substance at the external surface. Especially in senile eyes, the meshes of the network are packed with such deposits.

The findings suggest an age-dependent increase in the resistance to aqueous outflow from the ciliary body into the posterior chamber, localized in the basement membrane network at the internal surface of the nonpigmented epithelium.

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OPHTHALMIC MINIATURE

"It wasn't what she said," he reported later. "It was simply her attitude. There was something sly and suspicious about her. She just couldn't meet my eye. She wouldn't look at me."

"In Puerto Rico, a nice girl, a good girl," he explained, "does not meet the eyes of an adult. Refusing to do so is a sign of respect and obedience. It would be as difficult for Livia to look you in the eyes as it would be for her to misbehave, or for her mother to come to you with a complaint. In our culture, this is just not accepted behavior for a respectable family."

Julius Fast
*Body Language*

# ELECTROCAUTERY PUNCTURE OF THE TRABECULAR MESHWORK IN ENUCLEATED HUMAN EYES

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In 1958, Grant[1] systematically studied the microsurgery of the trabecular meshwork in enucleated human eyes, using the anterior chamber route. He found that the incised meshwork had no tendency to retract, and that simple incision into Schlemm's canal had little effect on the facility of outflow. Grant suggested that the flaps of incised mesh fell against the outer wall of the canal, blocking the ostia of the collector channels. This hypothesis was strengthened by the fact that excision of the meshwork did increase the facility of outflow. Total excision of the mesh decreased the resistance to outflow some 75%.

However, partial excision of the trabecular meshwork reduced the outflow resistance only in proportion to the amount of mesh removed, suggesting that there was little or no flow from the surgical site along Schlemm's canal. Grant proposed that the lax intact meshwork occluded the canal, preventing circumferential flow.

If there was a free path from anterior chamber to canal, the canal itself should offer very little resistance to circumferential flow. The present research was designed to establish the presence such a free communication path.

## MATERIALS AND METHODS

The basic method described by Grant[1] was used. A 5-mm trephine hole in the cornea of the enucleated human eye allowed access to the trabecular meshwork and observation under 25- or 40-power magnification. A small piece of fine polyethylene tubing was placed between the iris and lens to prevent their retrodisplacement, creating a consequent tension on the meshwork during perfusion. The hole was closed by a stainless steel fitting[1] through which the eye was perfused at known constant pressure. The steel fitting was removed, microsurgery of the trabecular meshwork was performed, and the fitting was replaced for test of the surgical result.

Electrosurgery of the trabecular meshwork was accomplished with a Cameron 225 radio frequency cautery. A bipolar electrode was made from a 23-gauge, 1.5-inch hypodermic needle with a 32-gauge copper magnet wire threaded through the bore and held in place with epoxy resin adhesive (Fig. 1). The needle was connected to the ground and the central wire to the coagulation outlet. The coagulation control was set at 2.5. Under visual control the electrode was introduced through the corneal aperture and placed against the trabecular meshwork. The foot switch was depressed for about two to three seconds. This treatment had three results: (1) A definite hole in the mesh was produced (Fig. 2); (2) permanent gas bubbles were evolved (occasionally a bubble in Schlemm's canal had to be milked through the diathermy puncture by stroking the mesh

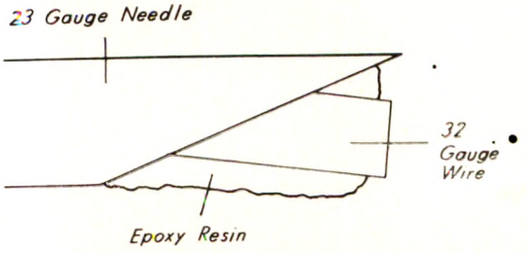



Fig. 1 (Moses). Schematic diagram of electrode tip.

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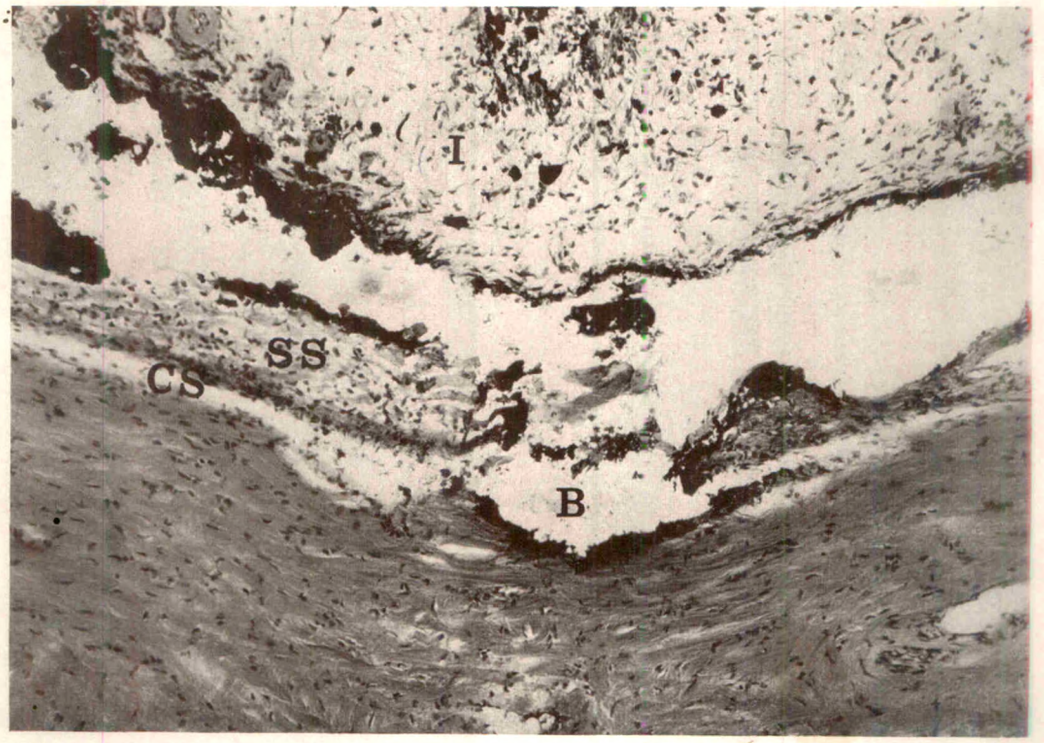



Fig. 2 (Moses). Burn through scleral spur into Schlemm's canal, frontal section. I = iris, SS = scleral spur, CS = canal of Schlemm, B = burn, partly occluded by debris.

with a blunt probe); (3) the cornea was distorted in the region of the burn.

A small iridodialysis was produced by grasping the iris with a fine forceps, the steel fitting was repositioned, and the eye again perfused through the fitting.

Detection of leaks around the steel trephine hole seal was by inspection through the microscope and by application of fluorescein solution as in Seidel's test.

## Results

Successful trabecular perforation increased the outflow facility by as much as 0.44 µl/min./mm Hg. Additional perforations did not usually increase the facility further (Table 1). The augmented facility tended to decrease with time. In one eye, for instance, the facility decreasing from 0.57 to 0.45 µl/min./mm Hg during 30 minutes, but remained constant at the lower figure for the next 15 minutes.

Marked increase of facility was finally achieved in seven of 13 eyes. From one to six electrocautery applications were required. In another eye (E71-249, Table 1), high facility (0.62 µl/min./mm Hg) was obtained initially after cautery, but in this eye was reduced after further cautery application.

## Discussion

The facility achieved by total removal of the trabecular meshwork, by one electrosurgical puncture, or by several electrosurgical punctures of the trabecular mesh is about 0.6 µl/min./mm Hg in those eyes in which the trabecular cautery appeared to function, suggesting that 0.6 µl/min./mm Hg is the facility of the collector channels and associated veins in the enucleated human eye. The fact that one perforation by heat can effectively remove the total resistance of the trabecular meshwork indicates: (1) that the perforation tends to remain patent in some eyes under

TABLE 1

EFFECT OF ELECTROCAUTERY OF THE TRABECULAR MESHWORK ON THE FACILITY OF OUTFLOW*
(μl/min./mm Hg)

| Eye | Facility before Cautery | Facility Following Cautery | | | | | |
|---|---|---|---|---|---|---|---|
| | | First | Second | Third | Fourth | Fifth | Sixth |
| E71-204 | 0.32 | 0.23 | 0.40 | 0.57 | | | |
| E71-185 | 0.28 | 0.33 | | 0.40 | | | |
| E71-183 | 0.12 | 0.14 | 0.15 | | 0.18 | | |
| E71-204 | 0.18 | | 0.34 | 0.30 | | | |
| E71-217 | 0.37 | 0.54 | 0.70 | | | | |
| E71-225 | 0.24 | 0.27 | 0.29 | 0.57 | | | |
| E71-226 | 0.33 | 0.37 | | 0.29 | 0.23 | 0.23 | |
| E71-227 | 0.28 | 0.27 | 0.25 | 0.27 | 0.27 | 0.29 | 0.50 |
| E71-228 | 0.27 | 0.37 | 0.37 | 0.49 | | | |
| E71-237 | 0.20 | 0.17 | 0.17 | 0.17 | 0.20 | | 0.16 |
| E71-245 | 0.22 | | 0.23 | | 0.27 | 0.24 | |
| E71-249 | 0.18 | | 0.62 | 0.33 | | | |
| E71-262 | 0.20 | 0.28 | 0.31 | 0.53 | | | |

* All perfusions were at 30 mm Hg and at room temperature.

the present experimental conditions, and (2) that flow along Schlemm's canal is free and of very low resistance when a free communication to the anterior chamber exists.

Schlemm's canal may break up into several channels[2] or may be occluded by endothelial proliferations in places.[3,4] The presence of these structural variations may account for some of the failures in this series.

## SUMMARY

Perforation of the trabecular meshwork by radio frequency electrocautery markedly increased the facility of outflow in seven of 13 enucleated human eyes. The facility achieved (0.40 to 0.70 μl/min./mm Hg) was of the same order as that found in an earlier investigation after complete removal of the trabecular meshwork by dissection, suggesting that flow along the canal of Schlemm is of low resistance.

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# LATE ENDOPHTHALMITIS AFTER FILTERING SURGERY

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Endophthalmitis occurring many years postoperatively is a little-emphasized, yet nearly always disastrous, complication of filtering surgery. The purpose of the present report is to describe nine such cases seen at the University of Illinois Eye and Ear Infirmary between 1966 and 1970, as well as two additional cases seen by staff consultants.

## SUMMARY OF CASES

The variety of types of underlying glaucoma present in our series of 11 cases is shown in Table 1. Seven had had thermal sclerectomies performed by alternately incising sharply and cauterizing the limbal wound until a fistula is made into the anterior chamber. Three patients had posterior lip sclerectomies performed with a Holth punch. Two or three bites of sclera were taken from the posterior lip in the manner described by Haas and Iliff.[1] A single pillar iridencleisis operation was performed on one patient. Tenon's capsule resections were not performed in any case. Ten of the 11 filtering blebs were described postoperatively as thin-walled and cystic, and their size ranged from one and one-half to three clock hours. Postoperative tensions ranged from 5 to 22 mm Hg with two eyes in chronic hypotony (Cases 7 and 8). The time elapsing between surgery and the onset of infection was from four months to 11 years. The average was 45 months.

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Eight patients presented with a one-day history of symptoms, usually consisting of pain, swelling, and redness of the affected eye. Although visual outcome was poor in all patients, the best final acuity among the three patients (Cases 1, 2, and 9) who waited three or more days before seeking medical attention was counting fingers at 10 inches. On initial examination, six patients had anterior chamber hypopyon and two had a hypopyon level in the bleb itself. There was anterior chamber flare and cells (but no keratic precipitates) in all cases. In one patient (Case 9), panophthalmitis with a fixed globe was present when he was initially seen. It was felt that the initial infection in this case occurred in the bleb and that panophthalmitis developed subsequently.

Cultures of the surface of the infected blebs were taken on all patients. Three of them grew staphylococci-coagulase positive, and one grew pneumococcus. The remainder of the cultures either grew diphtheroids or nothing. A diagnostic anterior chamber paracentesis was performed in one patient, but failed to reveal any organisms after culture.

Final visual acuity was markedly worse in all but three cases. In the eight in whom it worsened, the best final acuity was 20/100, while in the remainder it ranged from hand motions to no light perception. One eye was enucleated.

No other site of infection, trauma, or other intercurrent disease was detected by history or physical examination in this series of patients, with the exception of one patient who had well-controlled, adult-onset diabetes.

## DISCUSSION

Intraocular infection after filtering surgery has generally been thought to be associ-

TABLE 1

SUMMARY OF CASES

| Patient Age and Sex | Glaucoma (Type) | Surgery (Type-Date) | Post-Operative Tension (mm Hg) | Pre-infection Visual Acuity | Onset of Infection (Months Postop.) | Final Visual Acuity |
|---|---|---|---|---|---|---|
| 50-M | Open angle with angle recession | Thermal sclerectomy March, 1965 | 22 | 20/70 | 19 | CF |
| 45-M | Interstitial keratitis with secondary glaucoma | Iridencleisis June, 1961 | 12–15 | 20/200 | 66 | Poor light projection |
| 60-F | Open angle | Thermal sclerectomy February, 1963 | 10 | 20/30 | 47 | 20/100 |
| 60-M | Angle recession | Posterior lip sclerectomy March, 1967 | 18 | 20/100 | 34 | NLP, eye enucleated |
| 43-F | Open angle | Posterior lip sclerectomy September, 1969 | 16 | 20/70 | 4 | HM |
| 61-F | Chronic angle closure | Thermal sclerectomy July, 1965 | 19 | 20/100 | 55 | LP |
| 66-F | Heterochromic iridocyclitis with secondary glaucoma | Thermal sclerectomy May, 1966 | 5 | L.P. | 49 | LP |
| 26-F | Juvenile open angle | Thermal sclerectomy February, 1959 | 8 | 3/200 | 137 | 3/200 |
| 67-M | Open angle | Posterior lip sclerectomy September, 1968 | 20 | 20/200 | 23 | NLP |
| 58-F | Aphakic eye with glaucoma secondary to peripheral anterior synechiae | Thermal sclerectomy December, 1965 | 12–16 | 20/25 | 42 | 20/400 |
| 60-F | Open angle | Thermal sclerectomy June, 1967 | 8–10 | 20/20 | 25 | 20/40, scarred bleb |

ated primarily with the trephine operation. Indeed, most of the relevant literature[2-4] describes cases of this type. All but two of Sugar and Zekman's[2] reported 26 cases had been filtered by corneoscleral (Elliot) trephination. McGrand[5] reported two cases of infected blebs occurring three to four years after surgery. One of these patients had had a trephination (type unspecified), the other an anterior lip sclerectomy. Christensen and Robinson[6] reported nine cases of infected filtering blebs, but they did not indicate the type of surgery performed. One of their patients developed a filtering bleb following cataract surgery.

Since trephination is a procedure which has not been done in this institution for more than 10 years, no precise comparison could be made between the incidence of infection after trephination and after other types of fistulizing operations. It is sufficient to emphasize that intraocular infection is a very real late complication of any filtering operation and one that requires the prompt institution of the most vigorous antibiotic therapy.

The pathogenesis of this complication seems to be related directly to the type of filtering bleb produced and only indirectly to the type of fistulizing operation performed. Haas[7] has classified functioning filtering blebs into two types: Type I blebs are thin-walled and cystic, contain many septae, provide mainly transconjunctival drainage, have a positive Seidel test, and are very subject to breakage and infection. Type II blebs, on the other hand, are thick-walled, pale, with no visible vascularization, have a negative Seidel test, and provide mainly subconjunctival drainage.

Type I blebs are thought to be more frequent with an anterior dissection of the conjunctival flap, and this may be the reason for the association of the corneoscleral (Elliot) trephine operation with bleb infection in previous reports. Alternatively, this was the

most common type of operation performed at that time.

Older patients are thought to be more prone to the development of thin-walled blebs, since they have thinner Tenon's capsules. Anterior dissection of the conjunctival flap, so that it extends past the insertion of Tenon's capsule, will also increase the probability of a Type I bleb. In addition, the thermal sclerectomy has been implicated in the production of thin-walled blebs through the thermal destruction of Tenon's plexus at the time of surgery.[8]

In reviewing his results from filtering surgery, Haas[7,8] found an incidence of thin-walled blebs of 51% in posterior lip sclerectomies and 66% in iridencleisis operations. Exact figures indicating the incidence of thin-walled blebs in thermal sclerectomies are not available. However, since 10 of our 11 patients had thin-walled blebs, this suggests that they may have a much higher incidence of infection than thick Type II blebs.

The reported incidence of infection after filtering surgery ranges from 1% to 18%.[4] There were 520 filtering procedures performed at the University of Illinois Eye and Ear Infirmary from 1961 through 1970. Of this total, 302 were thermal sclerectomies, 182 were posterior lip sclerectomies, and 35 were done by iridencleisis. The incidence of infection was 1.5% for both thermal and posterior lip sclerectomies. The incidence following iridencleisis was 3%, but this is probably not significant statistically in view of the small number performed. More significant is the fact that all but one of these infections occurred in patients with thin-walled blebs.

While the Type II bleb is the one considered desirable, the Type I bleb is often obtained. Review of this series of patients suggests that it is this type which is most likely to provide a pathway for the entrance of microorganisms into the eye. It is apparent that the interior of the eye is in direct communication with the conjunctival sac through the Type I bleb, even though the way may be somewhat labyrinthine because of the septae in the blebs. Thus, any episode of conjunctivitis or blepharitis presents a serious threat to the eye of the patient with a Type I filtering bleb.

Elliot[9] felt that "an abrasion of the surface of the membrane" (of the filtering bleb) was necessary, in the presence of a conjunctival infection, to allow passage of microorganisms into the subconjunctival tissues. Robinson and Christensen[6] thought that the manipulation of gonioscopy was a contributing factor in one of their cases. In the case reported by Ashline and Ellis,[10] contact lenses were being worn by the patient at the time intraocular infection occurred.

None of the patients in our series were wearing contact lenses at the time infection occurred, nor had any of them been recently subjected to ophthalmic manipulation. No history of antecedent trauma of any sort was elicited. While manipulation or trauma may be a contributing factor in some cases, it is by no means a prerequisite for the development of these infections.

Leopold[11] has enumerated several nonocular conditions which may be contributory in the development of intraocular infection. These are: severe metabolic disease (such as uncontrolled diabetes), neoplastic disease, advanced age, or poor general health. None of these factors appear to be operative in our series. In addition, none of our patients had multiple surgical procedures or excessive surgical trauma, either of which might also predispose them to infection.

Prompt institution of treatment of even the mildest conjunctivitis is certainly mandatory in these patients, after obtaining a specimen for Gram stain, culture, and sensitivity. Control of chronic blepharitis should also be maintained. Patients with thin-walled blebs should be advised to contact their ophthalmologist at the earliest signs of redness or soreness of these eyes.

At the earliest suggestion of chemosis, pain, or unusually severe injection—and by all means if anterior chamber reaction is

present or purulent material is in the bleb—systemic as well as subconjunctival and topical antibiotic therapy should be instituted. Hospitalization affords a surer means of obtaining intensive therapy systemically as well as topically.

For the initial treatment of these patients, our present choice of systemic antibiotics is ampicillin or cephaloridine (methicillin should be added if there is suspicion of this being a resistant staphylococcal infection). Subconjunctival cephaloridine or gentamicin should be administered on daily or every other day basis, as well as a combination antibiotic solution such as Neosporin* at two-hour intervals. We believe this intensive initial antibiotic regimen is necessitated by the almost uniformly grim prognosis, as suggested by our cases.

Chandler[12] has recommended the use of prophylactic antibiotics twice daily in patients with thin-walled blebs and hypotonous eyes. Another prophylactic regimen might include the use of an antiseptic such as zinc sulfate 0.25% or benzalkonium chloride (Zephiran) 1:3000, or sulfa drops prophylactically.

Chandler considers hypotony to be a contributory factor in the development of these infections. However, in our series only two patients could be considered to have hypotonous eyes.

Arruga,[13] in discussing infection of filtering blebs, has stated, "seriousness is the characteristic of this complication." In our experience this is certainly not an understatement. Only three patients in our series escaped a marked loss of vision as a result of their infection. Two of these three cases had a pre-infection acuity of 3/200 and light perception, respectively, which remained unchanged; the other (Case 11) went from 20/20 with a functioning bleb to 20/40 with a scarred nonfunctioning bleb.

Although anterior chamber hypopyon is an ominous finding, we were not able to correlate its presence or absence with ultimate visual results as has been indicated in a previous study.[6] One of our patients (Case 8), who presented with hypopyon, had no change in visual acuity whereas two patients (Cases 1 and 3), who did not have hypopyon when originally seen, suffered marked loss of visual acuity.

In this article we have enumerated and reviewed only cases of late intraocular infection in patients whose surgery was intended to produce a filtering bleb. We have, in addition, seen six additional patients with intraocular infection which developed in eyes with filtering blebs which were the unplanned sequelae of cataract surgery. Ashline and Ellis[10] reported the development of endophthalmitis in such a patient who was, in addition, wearing contact lenses. An enucleation was the final result of a similar case reported by Dixon and his associates.[14] We feel, in view of this experience, that the possibility of an intraocular infection may be the strongest indication for repair of an unintentional filtering bleb following cataract surgery. This repair may be undertaken either surgically or, as Kirk[15] has recommended, by hyphrecation.

Although written in the pre-antibiotic era, Elliot's words regarding late infection following fistulizing operations serve as an appropriate reminder of the seriousness of this complication: "Under energetic treatment, full vision may, in rare cases, be restored; more often sight is permanently damaged, while a not uncommon event is the loss of all or nearly all vision, and even the eye as well."

## Summary

In 11 cases, intraocular infection occurred an average of 44 months after filtering surgery. Eight of these cases developed marked loss of vision. A thin-walled filtering bleb is thought to be the most common contributing factor to the development of infection. Anterior flap dissection, the use of thermal cau-

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tery, and advanced age of the patient are all factors thought to increase the incidence of thin-walled blebs. Trauma to the bleb was not a factor contributing to infection in this series of patients. Early, vigorous treatment of bleb infections is urged in order to prevent the disastrous result of intraocular infection. There is merit in the consideration of repair of large unintentional thin-walled blebs following cataract surgery to avoid this complication.

ACKNOWLEDGMENTS

We thank Drs. Morton F. Goldberg and Joseph Haas for their advice and encouragement in the preparation of this paper.

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OPHTHALMIC MINIATURE

Goya, after an illness at age 47, became deaf for the remaining 35 years of his life (probably from Vogt-Koyanagi syndrome) and all the gaiety and colour was lost from his paintings.

P. Trevor-Roper
*The World Through Blunted Sight*
New York, Bobbs-Merrill, 1970

# SERRATIA MARCESCENS ENDOPHTHALMITIS

JOHN F. BIGGER, M.D., GERALD MELTZER, M.D., ALAN MANDELL, M.D., AND RONALD M. BURDE, M.D.

*St. Louis, Missouri*

Serratia marcescens was first described by Bizio in 1823.[1] Subsequently, it became known as Bacterium prodigiosum because it produces a red pigment (prodigiosin). Recently, it has been recognized that nonpigment producing strains of Serratia marcescens also exist. The organism is a Gram-negative coccobacillus, presently classified in a division of the Enterobacteriacea with Klebsiella and Enterobacter. Criteria for identification of Serratia marcescens were established by Edwards and Ewing.[2]

Initially considered saprophytic for man, Serratia marcescens has in the past been intentionally sprayed in hospital environments to study airborne spread of bacteria.[3] Its red pigment has also been a useful marker in the study of bacteremia after dental extractions,[4] and bacteriuria after urinary tract procedures.[5] In recent years, however, Serratia marcescens has been increasingly implicated as an etiologic agent in severe human infections. It has been reported to cause respiratory and urinary tract infections, wound infections, meningitis, osteomyelitis, endocarditis, and septicemia.[6,7]

Reports of ocular infections by Serratia have been confined to purulent conjunctivitis,[8,9] lacrimal duct infections,[7] and corneal ulcers.[9,10] This paper reports two cases of severe purulent endophthalmitis from which Serratia marcescens was isolated.

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## CASE REPORTS

*Case* 1—A 44-year-old man was hospitalized on September 1, 1970, with an intraocular foreign body of the left eye. Six hours before admission he was struck in the left eye by a metal fragment while hammering a metal bolt. X-ray examination revealed a 4 × 7 × 2 mm foreign body located just beneath the wound of entry, 2 mm posterior to the nasal limbus. Vision was hand movements. A hyphema occupied approximately 15% of the anterior chamber and the intraocular pressure was 3 mm Hg. A vitreous hemorrhage obscured visualization of the retina. Operative exploration and foreign body extraction with a magnet through the site of entry was accomplished without difficulty. The wound was sutured. The patient was given an injection of aqueous penicillin, 100,000 units, and gentamicin sulphate, 6.8 mg, subconjunctivally at the conclusion of the procedure.

Thirty hours postoperatively the patient developed severe pain in his left eye, with a purulent conjunctival discharge, hypopyon, and drainage of purulent material from the wound site. In spite of therapy with methicillin and gentamicin systemically, and chloramphenicol and neomycin-polymixin-bacitracin topically, the infection continued to progress. Twenty-four hours later there was no light perception in the left eye, an early orbital cellulitis was present, and the patient was febrile. Enucleation was performed, the orbit was packed, and with continued antibiotic therapy the patient recovered and was discharged on September 10, 1970.

Cultures from the conjunctival sac and from the intraocular contents grew a nonpigmented organism identified as Serratia marcescens. The organism was sensitive in vitro to ampicillin, tetracycline, gentamicin, chloramphenicol, streptomycin, kanamycin, and polymixin B, and was resistant to cephalothin and cephaloridine.

Histologic examination (Fig. 1) revealed infiltrations of acute inflammatory cells within the cornea, anterior chamber, iris, ciliary body, vitreous, choroid, and retina. Blood was present in the anterior chamber and vitreous. There was severe destruction of the retina by the inflammatory process. Gram stains revealed large numbers of Gram-negative rods within the vitreous.

*Case* 2—An 85-year-old woman was admitted on September 16, 1970, for a cataract extraction in the left eye. Intracapsular cataract extraction was accomplished without vitreous loss. At the conclusion of the procedure a subconjunctival injection of aqueous penicillin, 100,000 units, and gentamicin sulphate, 6.8 mg, was given. Twenty-four hours after surgery the cornea had minimal striate kerato-

tions during or after the use of antibiotics, including antibiotics to which the organism is susceptible, in vitro, may necessitate re-evaluation of the concept of prophylactic antibiotics if such infections become common in ophthalmology.

The second feature of Serratia which is of considerable significance is the in vivo resistance of the organism to antibiotic therapy. The high mortality rate of Serratia septicemia attests to the significance of this fact.[6] In vitro testing of antibiotic sensitivity may reveal multiple sensitivities, most commonly to gentamicin and kanamycin,[6] and these are recommended as the antibiotics of choice. In our cases, however, in spite of antibiotic therapy there was rapid progression of the infection. The in vivo resistance of Serratia marcescens is attributed by Miller and Buckler[12] to the ability of the organism to continue to proliferate intracellularly after phagocytosis by white blood cells. The proliferating organism intracellularly is thus not affected by the extracellular concentration of antibiotics. This feature of intracellular survival is apparently responsible for the virulence of the infecting organism and its in vivo resistance to therapy.

## Summary

In two cases reported, severe purulent endophthalmitis was caused by Serratia marcescens. Serratia infections are prone to occur in individuals with debilitating conditions, with altered host resistance, following surgery, and where antibiotics have been in use. Infections with this organism show an in vivo resistance to antibiotic therapy. Although reports of ocular involvement are rare, three instances of Serratia infection have been associated with the use of the soft contact lenses.

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# HETEROGENEITY OF DISORDERS IN PATIENTS WITH CORNEAL CLOUDING, NORMAL INTELLECT, AND MUCOPOLYSACCHARIDOSIS

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Eight years ago, we reported a series of patients with corneal dystrophy, excessive excretion of urinary acid mucopolysaccharides (AMPS) and variable, although generally not severe, systemic abnormalities.[1] Certain of their clinical manifestations had a considerable resemblance to the sublethal hereditary syndrome of Hurler. However, most of our patients displayed no features tending to affect longevity and usually they had normal intelligence; some were married and gainfully employed despite their visual impairment.

With a renewed interest in the mucopolysaccharidoses, several investigators attempted to subdivide these disorders into distinct genetic types.[2-4] McKusick and associates,[4] in their classification, referred to our series of patients (adding their own cases) as mucopolysaccharidosis type V, or Scheie's syndrome. Recently, Wiesmann and Neufeld[5] stated that the patients with type V mucopolysaccharidosis are biochemically indistinguishable from patients with Hurler's syndrome. It became, therefore, important to reevaluate those of the currently available patients whom we originally described, utilizing recently developed biochemical methods and bringing up to date radiological and clinical findings.

From the Section on Child Neurology, National Institute of Health (Drs. Constantopoulos and Dekaban), and the Department of Ophthalmology, University of Pennsylvania Hospital (Dr. Scheie).

Reprint requests to Harold G. Scheie, M.D., Department of Ophthalmology, University of Pennsylvania Hospital, Philadelphia, Pennsylvania 19104.

## MATERIALS AND METHODS

Four patients whose initial diagnosis was corneal dystrophy are the subject of this study. Refrigerated (0–4°C) 24-hour urine specimens without addition of preservatives were used for the isolation of AMPS. From the undialyzed urine, AMPS were precipitated with cetyl pyridinium chloride (CPC) and also by chromatography of Ecteola (chloride form).[6] The differences in recovery of AMPS by these two methods was never greater than 10%.

Hexuronic acid content of the isolated AMPS was measured by the carbazole reaction,[7] the orinol method,[8] and the borate-modified carbazole method.[9] Hexosamine was determined by the Elson-Morgan reaction[10] and galactosamine was assayed enzymatically.[11] Sulfate was determined by the method of Antonopoulos[12] and N-sulfate hexosamine according to Lagunoff and Warren,[13] without prior hydrolysis of AMPS. The AMPS were subjected to paper electrophoresis.[14] Construction of elution diagrams by gel filtration on Sephadex G-200 and determination of the distribution of molecular weights of the AMPS was performed as previously described.[15] The conditions for the enzymatic hydrolysis of chondroitin sulfate A (CSA), chondroitin sulfate B (CSB) and chondroitin sulfate C (CSC) with chondroitinase-AC and -ABC were those used by Saito, Yamagata, and Suzuki[16]; heparitin sulfate (HS) is not affected by these enzymes.

## Case reports

*Case* 1—This 39-year-old man (T.L., Fig. 1) and his married sister (R.L.W.) were described previously.[1] His general health was good in all respects until he reached five years of age, when he gradually developed what was considered to be arthritis of the hands and feet. Inguinal herniorrhaphies were performed at the age of four and eight years. Impairment of vision was first noticed in his early twenties; this was soon followed by complete inability to read. Examination disclosed cardiac enlargement with harsh systolic and diastolic murmurs and also enlargement of the liver and spleen. The interphalangeal joints (particularly the terminal) of both hands were swollen and ankylotic (Fig. 2), and the wrists were deformed. The findings were not compatible with those of the carpal tunnel compression of the median nerve. Similar, although less marked, abnormalities were present in his feet. The acuity of vision in 1958 was RE: 6/150, LE: 6/100 without correction, but in 1970 he could perceive only hand movements (Fig. 3). Slit-lamp examination revealed diffuse stromal corneal clouding, most marked at the periphery of the corneas. The deeper layers seemed more involved than the superficial. Epithelial edema was absent, but the corneas were at least one-fourth more than normal thickness. During 12 years of observation the central haziness became more marked. Pigment changes were never seen in the fundi. Visual impairment was attributed to the corneal changes. Visual fields were full to 5/330 white. Electroretinography was never done. The patient's hearing was serviceable, although the audiogram showed 45% loss of pure tones between 3000 and 6000 frequencies. Intelligence examination gave him verbal quotient above 120.

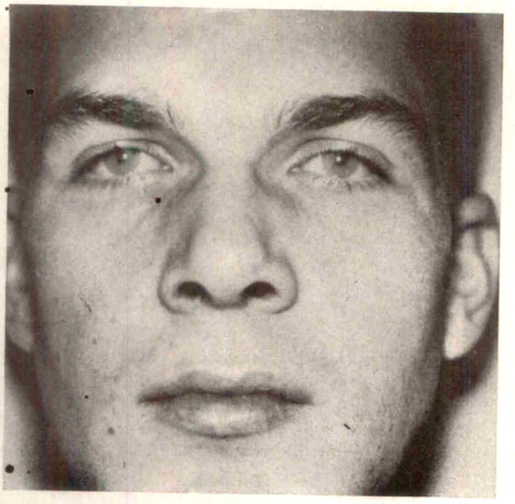


Fig. 1 (Constantopoulos, Dekaban, and Scheie). Case 1 in 1958 when referred for consideration of keratoplasty because of a diagnosis of familial corneal dystrophy.



Fig. 2 (Constantopoulos, Dekaban, and Scheie). Case 1. Patient's hands showing deformity of fingers.

The x-ray films of the skeleton were unusual: distal articular surfaces of radii were deformed; the carpal bones were small and contained cystic lesions; the distal ends of the metacarpals had curious pyramid-shaped deformities and the phalanges showed flexion-type deformities (Fig. 4-A). Similar, although less severe, abnormalities were present in his feet (Fig. 4-B). In addition, the vertebral bodies were moderately flattened (Fig. 5) and ribs were considerably widened (spatulated) posteriorly. The abnormalities in the wrists and hands were considered unique and not typical of Hurler's syndrome.

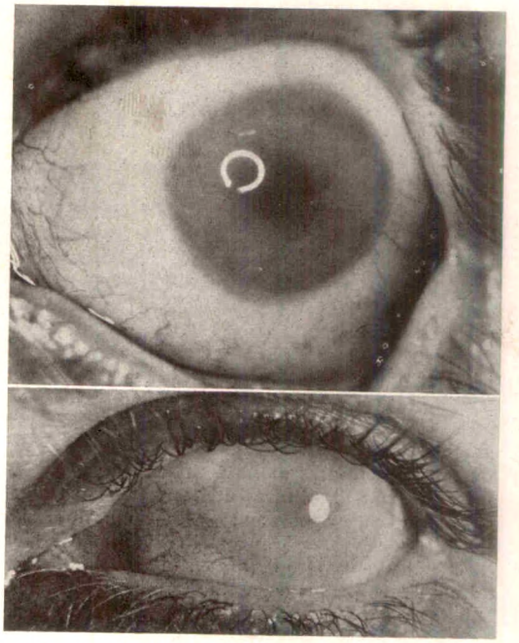


Fig. 3 (Constantopoulos, Dekaban, and Scheie). Case 1. Top: Left eye of patient in 1958, showing diffuse corneal haze. Bottom: Left eye of patient in 1970, showing more marked central haziness.

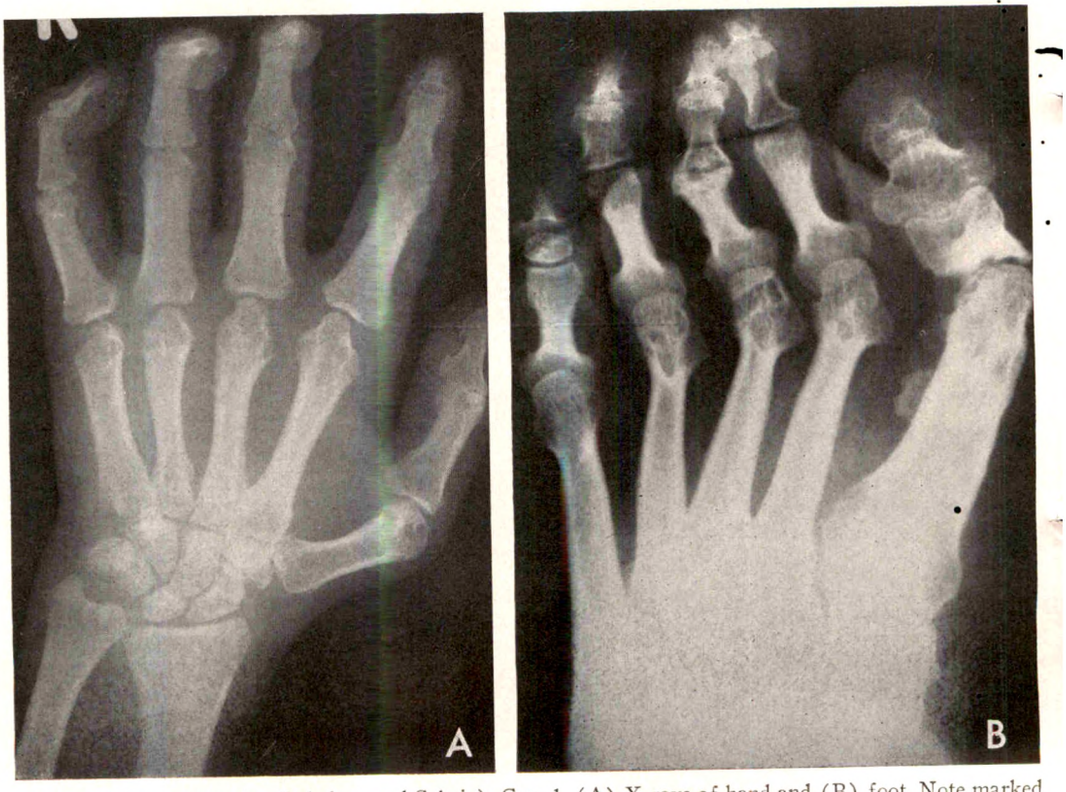



Fig. 4 (Constantopoulos, Dekaban, and Scheie). Case 1. (A) X-rays of hand and (B) foot. Note marked contracture deformities of terminal phalanges, unusual pyramid-like distal ends of metacarpals, cystic lesions, especially in the carpal bones, and growth abnormalities. However, tapering of proximal ends of metacarpals and other abnormalities typical of Hunter-Hurler's syndrome are absent.

*Case 2*—This 37-year-old woman (Fig. 6) is the affected sister of T.L. (Case 1) and has impaired vision from long-standing corneal opacities. In 1958, after an unsuccessful keratoplasty, her vision was RE: hand movements, LE: 6/24, and she had taken to counting fingers. The ocular findings and their subsequent course (Fig. 7) were identical to those of her brother, except for an opaque corneal graft. For a number of years she has had considerable limitation of movement in hands and feet. Her menses began at the age of 12 years and have been regular. Currently, she is married and has done some gainful work intermittently. On examination, she was found to have an excessive number of pigmented moles with some areas of depigmentation and a few cutaneous telangiectases. She had apical systolic and diastolic murmurs and markedly enlarged spleen and liver (Fig. 8). Her hands and wrists were deformed (Fig. 9) with typical ankyloses in flexion of the terminal phalanges. Radiologic surveys of the skeleton revealed essentially similar findings as in her older brother. The carpal bones were cystic in appearance and the metatarsals were short, but they did not have the characteristic proximal tapering usually seen in Hurler's syndrome. The metacarpal heads were conical and contained small cystic lesions; the terminal phalanges were in flexion ankylosis (Fig. 8). The radial styloid processes were underdeveloped bilaterally. The ribs had broad, spatulated midportion segments; the spine and skull were essentially normal. Except for the spatulate appearance of the ribs, it was the conclusion, on radiologic evidence, that the bony lesions were quite unique in both siblings and not typical of Hunter-Hurler's syndrome.

*Case 3*—This patient (A.B.[3]) is a white girl currently 12 years of age. She has developed somewhat coarse facial features, with thick lips, flattened bridge of the nose and prominent eyebrows (Fig. 10). Her gestation, delivery, and infancy were normal. She sat alone at six months, walked at 13 months and spoke in sentences at three years of age. At about that time she developed contractures in her finger joints and limitation of movement in elbow and shoulder.

While her maternal great-grandmother and great-grandfather are second cousins, this child's parents and younger sibling are alive and well.

On examination, both corneas were diffusely hazy. Her vision in 1961 was RE: 6/12, LE: 6/12, and in 1970, RE: 6/150, LE: 6/20. Findings on slit-lamp examination were identical to those in Cases 1

and 2, except that in this patient the corneal clouding seemed more uniform peripherally and centrally (Fig. 11). Fundi were normal. She had a Grade II systolic murmur over the precordium and a small umbilical hernia. Her liver was moderately enlarged. Her fingers, and especially the terminal phalanges, were in flexion deformity (Fig. 12), and she had limitation of movement in elbow and shoulder joints. Radiologic examination in 1960 showed flexion deformities in the phalangeal joints (Fig. 13) and evidence of delayed maturation of bones. The vertebral bodies were normal.

*Case 4*—This boy (J.M.[1]) is currently 18 years of age (Fig. 14). He was first examined at the age of 10 months for haziness of both corneas; this was considered then to represent congenital idiopathic edema of the corneas. At the age of one year, bilateral inguinal hernias were repaired. At the age of 10 years his height was 56.5 inches and his weight was 69 pounds. He had a Grade II apical systolic murmur, and his hands were somewhat broad (Fig. 15). Both corneas had a diffuse haze with the density greater in the deeper layers. Visual acuity as-



Fig. 5 (Constantopoulos, Dekaban, and Scheie). Case 1. Note some flattening of vertebral bodies and increase in concavity of intervertebral surfaces. There is no kyphosis and only mild spur formation.

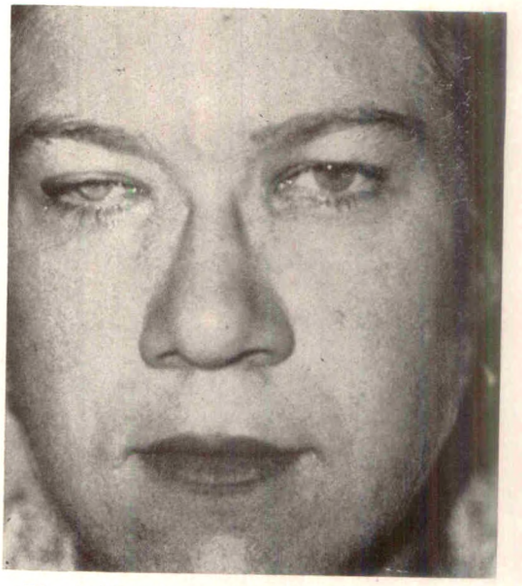


Fig. 6 (Constantopoulos, Dekaban, and Scheie). Case 2, sister of patient T.L. (Case 1), seen in 1958 becaused of so-called corneal dystrophy.

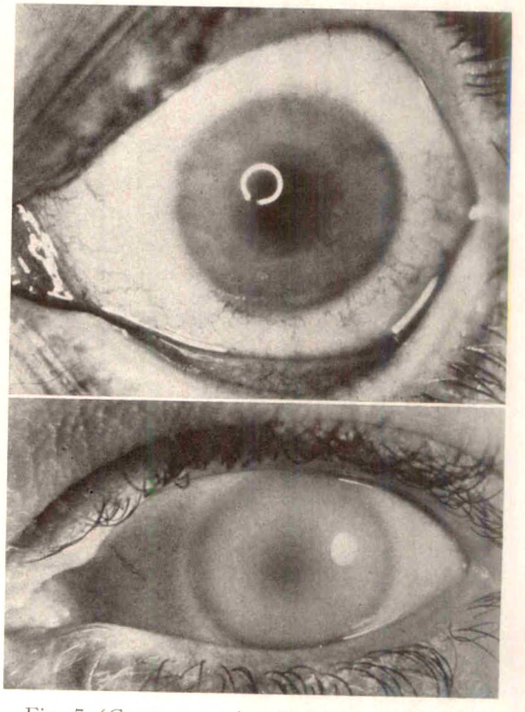


Fig. 7 (Constantopoulos, Dekaban, and Scheie). Case 2. Top: Left eye of patient in 1958, with evident cloudiness of cornea. Bottom: Same eye in 1970, showing opaque corneal graft.

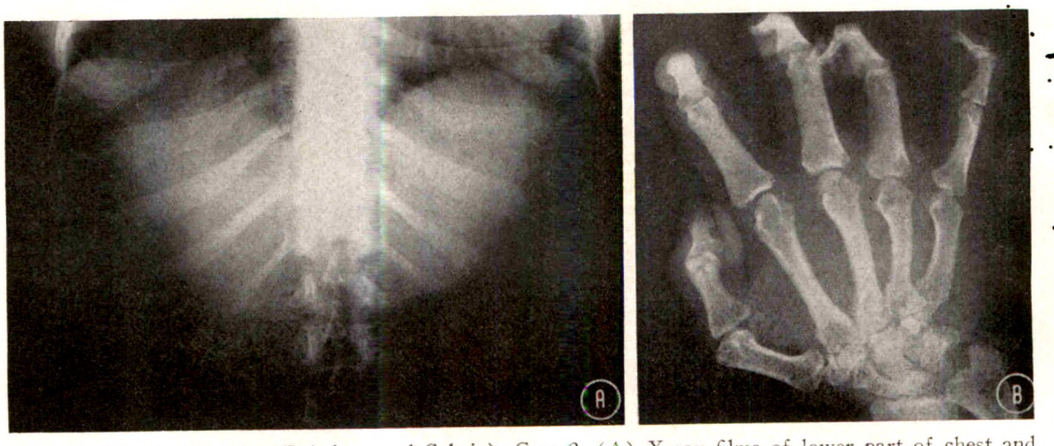


Fig. 8 (Constantopoulos, Dekaban, and Scheie). Case 2. (A) X-ray films of lower part of chest and upper part of abdomen. Note greatly enlarged liver and spleen and spatulate midportion of ribs. The spine is normal. (B) X-ray films of hand showing similar, although slightly milder, abnormalities as seen in patient's older brother (Case 1).

sessment in 1956 was unreliable; in 1970, it was RE:6/60 and LE: 6/100 with a more marked corneal haze (Fig. 16). The boy's mental status is normal. The parents and two siblings are alive and well.

## Discussion

The first three patients have remarkably similar clinical features. They share, in common with Hurler's patients, corneal opacity and hepatosplenomegaly, but differ from them in having normal intelligence, essentially unaffected longevity, relatively normal height and distinct skeletal abnormalities.

The fourth patient is essentially healthy in all respects, except for corneal opacity discovered when he was one year of age. Thus, this patient may represent an entirely different diagnostic problem.

The visual acuity in all four of these patients has diminished due to increased corneal clouding. Pigmentary degeneration of the retina was not seen, nor was optic atrophy. Visual fields were not studied, except by confrontation, nor was electroretinography performed. The fundi were normal when these could be visualized; in Cases 1 and 2 marked blurring of vision precluded good visualization.

In Table 1, the content and composition of urinary AMPS are analyzed and the results in our four patients are compared with those of 11 normal controls and a patient with proven Hurler's syndrome. In normal controls the average content of 24 hour urinary AMPS was 10.1 mg (range 4.5–16.5) and in the patient with Hurler's syndrome it was 117.0 (range for six similar Hurler's patients was 100–125 mg). The first three patients (Case 1–3) had currently 137, 108, and 162 mg AMPS in 24-hour urine, respectively while the fourth (Case 4) had only 9 mg AMPS. Thus, the total urinary AMPS in the patient with Hurler's and in the first three of our four patients was greatly elevated and within the range seen in Hurler's syndrome, whereas the total urinary AMPS of the fourth patient (Case 4) was within normal range.

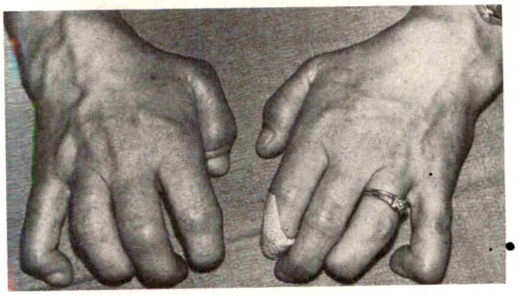


Fig. 9 (Constantopoulos, Dekaban, and Scheie). Case 2. Patient's hands and wrists in 1970, with typical ankyloses in flexion of terminal phalanges.



Fig. 10 (Constantopoulos, Dekaban, and Scheie). Case 3. Left: Patient as first seen in 1966. Right: Same patient when seen in 1970.

The composition of AMPS (Table 1) in the normal controls consisted of about 72% of CSA + CSC, 21% HS, 3.6% CSB and a small remainder of KS, the carbazole/orcinol ratio (C/O) being 1.31. In the patient with Hurler's syndrome, the greatest contribution to the urinary AMPS was by CSB (68.5%) and HS (26.5%); the CSA+CSC amounted to only 4.9% and C/O ratio was 0.65. The siblings (Cases 1 and 2) had quite similar composition of AMPS, and in both cases, the composition was not very much different than that seen in Hurler's disease patients, but the patient identified as Case 3 had grossly different composition of AMPS,

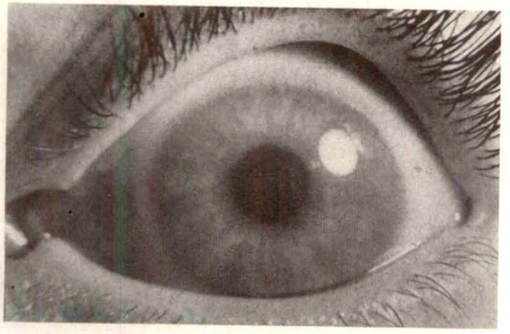


Fig. 11 (Constantopoulos, Dekaban, and Scheie). Case 3. Left eye showing uniform corneal clouding peripherally and centrally.

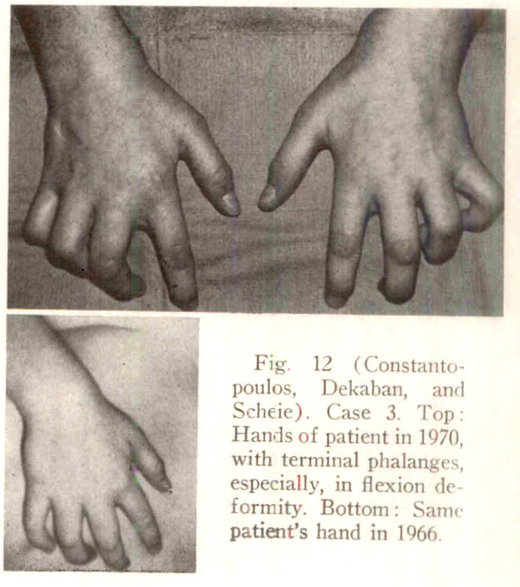


Fig. 12 (Constantopoulos, Dekaban, and Scheie). Case 3. Top: Hands of patient in 1970, with terminal phalanges, especially, in flexion deformity. Bottom: Same patient's hand in 1966.



Fig. 13 (Constantopoulos, Dekaban, and Scheie). Case 3. X-ray film of right hand and wrist. The flexion deformities of phalanges are pronounced. The elongation of distal ends of metacarpal is in an early phase as compared to older patients (Figs. 4 and 8). Also there is evidence of delay in bony maturation.

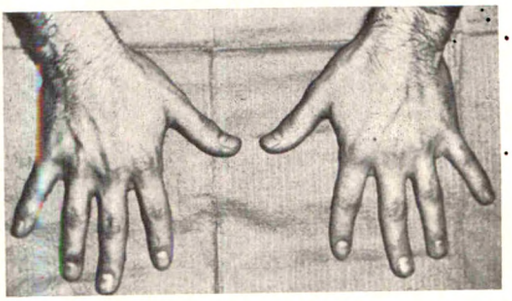


Fig. 15 (Constantopoulos, Dekaban, and Scheie). Case 4. Broad, spadelike hands.

with HS amounting only to about 8% while CSB constituted about 90% of the total. The composition of urinary AMPS of the fourth patient (Case 4) was similar to that of the normal controls.

Complete analytical data of the urinary AMPS in the normal controls and in the patients studied are given in Table 2. It may be seen that the contents of galactosamine, glucosamine and N-sulfate hexosamine, as well as the C/O ratios indicate the substantial presence of HS (about 30% of the total urinary AMPS) in the first two patients

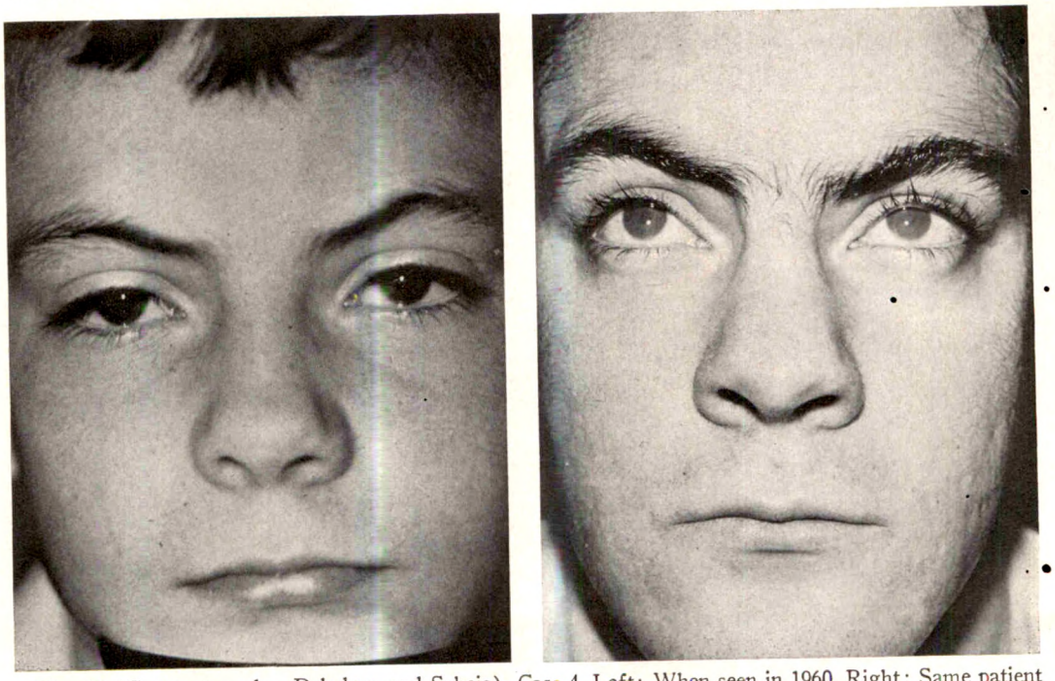


Fig. 14 (Constantopoulos, Dekaban, and Scheie). Case 4. Left: When seen in 1960. Right: Same patient in 1970.

(Cases 1 and 2), while the third patient (Case 3) excretes very little HS (less than 10% of total AMPS).

Five mg of urinary AMPS from all patients except Case 4 were incubated in total volume of 2.5 ml, with 0.5 units chondroitinase-ABC for three hours. At the end of the incubation, the mixture was inactivated for three minutes in boiling water and the AMPS were isolated with the aid of 1.0 g Ecteola chloride column. The recovered AMPS (measured as uronic acid) were 38, 34, 7.5, and 19% of the AMPS from Cases 1–3 and the patient with known Hurler's disease (Case 5), respectively. The carbazole/orcinol ratio was 1.4, 1.3, 1.8, and 1.45, compared to 0.76, 0.75, 0.47, and 0.65 of the original AMPS. The last values (except the third one) are much lower than the values obtained with standard heparitin sulfate and the urinary HS from Sanfilippo (ratio 1.8–2.5). After a second digestion with chondroitinase-ABC, the AMPS mixture was applied to a Sephadex G-200 column, but no further production of unsaturated acetylgalactosamine-containing disaccharides was noted. In separate experiments it was found that the molecular weight distribution of HS after incubation with chondroitinase-ABC was not changed; finally, after incubation of 250 μg of urinary AMPS from Case 4 with the above enzymes, only a small amount of a

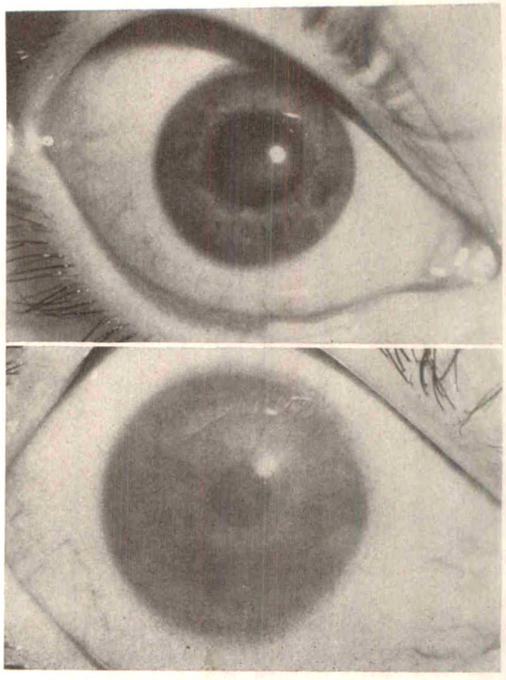


Fig. 16 (Constantopoulos, Dekaban, and Scheie). Case 4. Top: Left eye of patient showing diffuse corneal haze in 1960 (visual acuity unreliable). Bottom: Same eye in 1970, with corneal haze considerably more marked.

TABLE 1

TOTAL VALUES AND COMPOSITION OF URINARY AMPS IN NORMAL CONTROLS, PATIENTS WITH HURLER'S SYNDROME, AND FOUR PATIENTS REPORTED

| Subjects | 24-Hour Volume (ml) | Sex and Age (in years) | Urinary AMPS (mg/24 hours) | C/O Ratio | Estimated Composition (HS:CSB:CSA +CSC) |
|---|---|---|---|---|---|
| Normal controls (six boys, five girls) | | M-4-17 | range 5.2–19.5 | — | — |
| | | F-4-17 | range 4.5–18.0 | — | — |
| Normal adult male controls (pooled) | | — | — | 1.31 | 21.0:3.6:72.6† |
| Present cases: | | | | | |
| Case 1 | 2362 | M-39 | 137.0 (41.6)* | .76 | 32:63.0:5.0 |
| Case 2 | 967 | F-37 | 108.0 (32.1) | .74 | 30:65.0:5.0 |
| Case 3 | 350 | F-12 | 162.0 (29.0) | .45 | 8.0:90:2.0 |
| Case 4 | 870 | M-18 | 9.0 (3.5) | 1.13 | 15:5:80 |
| Patient with known Hurler's syndrome | 420 | M-2 | 117.0 (30.5) | .65 | 26.5:68.5:4.9‡ |

* Number in brackets is uronic acid content in mg/24 hour urine.
† Plus small remainder of KS, the carbazole/orcinol ratio being 1.31.
‡ Carbazole/orcinol ratio 0.65.

TABLE 2

ANALYSIS AND COMPARISON OF URINARY AMPS IN PATIENTS STUDIED AND NORMAL CONTROLS

| | Hexuronic Acid | | Hexosamine | Gal $NH_2$/GLU NHe | Sulfate | N-Sulfate (% equiv. Hep.) |
|---|---|---|---|---|---|---|
| | Carbazole* | Orcinol | | | | |
| Normal controls | 35.5 | 27.0 | 29.5 | 74/26.0 | 13.5 | — |
| Present cases: | | | | | | |
| Case 1 | 21.9 | 26.5 | 25.0 | 70/30 | 12.3 (.92) | 22.0 |
| Case 2 | 28.4 | 37.3 | 34.0 | 71/29 | 15.9 (.89) | 20.0 |
| Case 3 | 18.3 | 34.4 | 30.0 | 93/7 | 14.8 (.92) | 10.0 |
| Case 4 | 13.7 | 13.3 | 11.6 | N.S. | 12.7 | <10.0 |
| Patient with Hurler's syndrome | 21.9 | 33.6 | 31.3 | 73.5/26.5 | 17.3 | — |

* Dische method.

substance with electrophoretic mobility of heparitin sulfate was left intact.

A recently developed method[15] of gel filtration for the determination of molecular weight distribution and composition of the AMPS was applied to the isolated AMPS from the patients' urines.

Figure 17 shows the elution diagram profiles and chemical reactivities of the urinary AMPS from our patients and from normal controls. Urinary AMPS from normal subjects give the elution pattern shown in the bottom panel. The average molecular weight is about 14,000 and the distribution is fairly symmetrical on both sides of the peak. The chemical reactivities reflected those of the predominant components (CSC and CSA). The elution diagram from the urinary AMPS of patients with Hurler's syndrome is bimodal (second panel from bottom). The peak at the left is about 40% of the total AMPS, consists of CSB, and has an average molecular weight about 18,000. The larger peak at right is about 50% of the area of the diagram and its AMPS consist of CSB and HS. The average molecular weight is about 6,000. The average molecular weight of the total AMPS from this patient is about 11,500. The upper two panels represent the elution diagrams of the two siblings (Cases 1 and 2). It is of interest that they are *not* bimodal and that they show considerable shifting towards the small molecular weights. About 80% of the AMPS, consisting of CSB and HS, are highly degraded. The rest is mainly CSB of intermediary molecular weight. The average molecular weight of the total AMPS from these two patients is about 8,000. In contrast to these, the urinary AMPS of Case 3 (third panel from top) are of large molecular weight; about 60% of the AMPS are pure CSB, with an average molecular weight of about 20,000. There is, however, some HS as indicated from the C/O ratio at the extreme right end of the elution diagram. The average molecular weight of the AMPS from this patient is about 15,500. Thus, the AMPS of the two siblings (Cases 1 and 2) and the patient identified as Case 3 differ from those of the patients of Hurler, Hunter, and Sanfilippo.[15] Finally, the elution diagram of the urinary AMPS from the fourth patient (Case 4) closely resembles the diagram of normal controls.

## CONCLUSIONS

Detailed evaluation of the clinical and biochemical data on the four patients reported here, in whom the common denominator of corneal opacity, indicates that we are probably dealing with heterogeneity. It is unlikely that mucopolysaccharidosis is the cause of the corneal opacity in Case 4, and the etiology in this case remains to be determined. It is evident that the clinical and radiologic findings in the remaining three patients are similar, while the composition and molecular weight distribution of their urinary AMPS are different. Three clearly evident problems require more detailed consid-

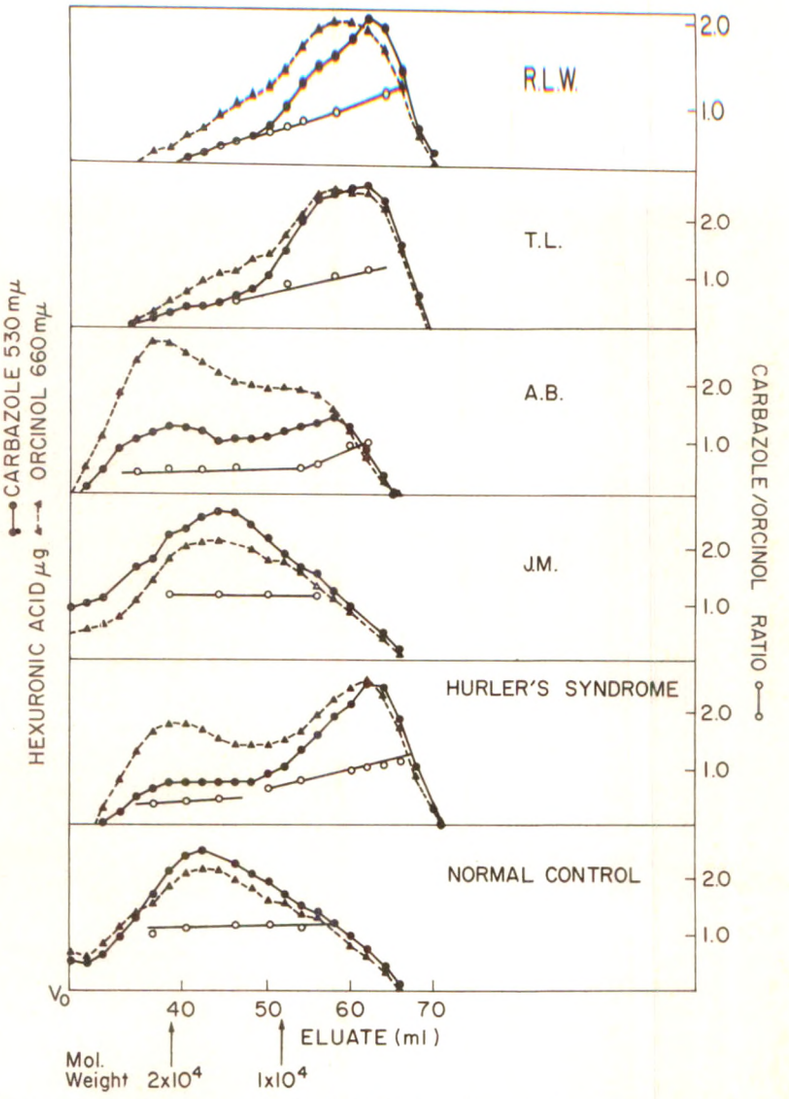



Fig. 17 (Constantopoulos, Dekaban, and Scheie). Elution diagrams in a normal control, typical Hurler's disease patient, and in the four patients reported here.

eration: (1) There is a need to determine the composition and characterization of urinary AMPS in the patients generally classified as having mucopolysaccharidosis V or Scheie's syndrome (Cases 1–3). (2) The question of nosological relationship between mucopolysaccharidoses I and V must be resolved. (3) The significance of the different composition and distribution of molecular weights of AMPS in Cases 1 and 2 as compared to Case 3 requires clarification.

In this study it was found that the urinary AMPS of the two siblings (Cases 1 and 2, the classic Scheie patients) consist of CSB and HS in the ratio of about 70:30, which is characteristic of the Hurler patients. The presence of HS in the urinary AMPS of these two patients was noticed by Terry and Linker,[2] and by Kaplan.[17] The low carbazole-to-orcinol ratio of the HS isolated by us after removal of other AMPS by enzymatic hydrolysis is similar to that of the HS from

the urinary AMPS of a patient with polydystrophic dwarfism,[18] but we have no explanation for this. Of special interest is the drastic shift of the urinary AMPS towards the low molecular weights in these two siblings. The fact that the CSB from their urine is of very small molecular size could explain why Terry and Linker[2] were unable to demonstrate the presence of CSB that precipitates, as the calcium salt with 10 and 20% alcohol concentration, as was the case with the CSB from their Hurler patients.

The second problem is the relationship of the type V mucopolysaccharidosis, as exemplified by the first three patients, to Hurler's syndrome. The elution patterns obtained by gel filtration of the urinary AMPS of the two siblings (Cases 1 and 2) are different not only from those of patients with mucopolysaccharidoses types I, II, and III,[19] but we have found in our laboratory (unpublished data) that they are unique among many such patterns from other mucopolysaccharidoses and from those of patients with various other diseases. If these questions were resolved, the elution pattern could then be a useful tool for characterization and classification of disorders with abnormal metabolism of AMPS. The experiments in tissue culture fibroblasts from the skin of these two siblings and from the skin of patients with Hurler's disease performed by Wiesmann and Neufeld[5] must be taken into consideration, but the definitive decision about nosological identity of these disorders cannot depend on this finding alone. Apparently, the fibroblasts from these two variants behaved metabolically as if they were lacking the same agent. However, the question remains: How far can one generalize from the experiments with mixed populations of fibroblasts in tissue cultures to the metabolic complexity of the human organism? The clinical and laboratory differences between the cases currently classified as type I and V mucopolysaccharidosis appear to be too great to consider types I and V as the same disease. A majority of patients with Morquio's syndrome have normal mentality, and a small proportion may have fine corneal opacity; their clinical features, however, are quite different from those of patients with other mucopolysaccharidoses. Likewise, Maroteaux-Lamy syndrome is clinically and radiologically distinct.

The third problem relates to the differences of physical characteristics of AMPS between Cases 1, 2, and 3. The presence of difference in composition and elution patterns between Cases 1 and 2, on the one hand, and Case 3 on the other, complicates further existing classifications. The possible explanation of this particular discrepancy could be the age difference; the siblings (Cases 1 and 2) are in their late thirties while the other patient (Case 3) is presently only 12 years of age. Unfortunately, we do not know the composition of urinary AMPS in Cases 1 and 2 prior to their adult years. Kaplan[18] computed the ratio of CSB : HS as 65 : 35 and 68 : 32 at their respective ages of 32 and 30 years; currently this ratio for both the brother and sister was determined to be 64 : 31. Possibly, with increasing age and after reaching adulthood, both the composition and molecular weights of AMPS could become altered; no information on this aspect is available. Other explanations, such as a presence of particular modifying genes in certain families with this syndrome, or altered general body metabolism, should also be considered. Our finding that the AMPS are of small molecular size in these patients could conceivably lead to easier elimination from their organs of excessive amounts of AMPS and thus could affect the manifestation of the disease. However, the CSB in Case 3 is of large molecular size, and yet this patient has normal mentality.

Since our knowledge of life histories, pathology, biochemistry, and enzymatic defects involved in various mucopolysaccharidoses is incomplete,[20] it appears advisable to exercise considerable conservatism in proposing further classifications of these syndromes. Accumulation of a larger pool of patients with

these disorders, along with detailed clinical and pertinent laboratory data, will eventually permit resolution of existing controversies. We feel that for the time being it is advantageous to retain types I (Hurler) and V (Scheie) of mucopolysaccharidosis as possibly separate syndromes, since they differ markedly in their clinical manifestations, radiologically demonstrable skeletal abnormalities, and in the distribution of molecular weights of urinary AMPS.

## Summary

Four patients from an earlier series, and classified at that time as having type V mucopolysaccharidosis, were re-evaluated, using currently available, newer techniques. In this original series of patients the common denominator was corneal opacity and normal intelligence. On the basis of marked differences in the clinical manifestations and laboratory findings, it is suggested that for a defined portion of these patients the classifications of type I (Hurler's disease) and type V mucopolysaccharidosis (Scheie) be retained as possibly separate syndromes. The elution diagrams of molecular weight distribution of acid mucopolysaccharides provide a useful tool for characterization of various mucopolysaccharidoses.

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# CARCINOID SYNDROME WITH BILATERAL ORBITAL METASTASES

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Carcinoids are slowly growing malignant neoplasms which metastasize in 21 to 75% of the cases. They originate from the enterochromaffin or Kultschitsky cells in the intestinal tract; other primary sites include the bronchi, bile ducts, pancreas, and ovary.[1]

Wong and Melmon[2] have previously reported the ophthalmic manifestations of the carcinoid syndrome. These consist of flushing of the head, neck, and arms after a provocative intravenous injection of epinephrine. Associated conjunctival vascular dilatation and lacrimation are constant early signs of the flush. Ten of 16 patients had a variety of fundus changes which were attributed to carcinoid syndrome.

The present case report is of interest because the presenting ophthalmic complaint of the patient was diplopia and a mass under her right eye. Subsequently, a diagnosis of an unsuspected carcinoid tumor with bilateral orbital metastases was made by histopathologic examinations, provocative epinephrine tests, and chemical assays of tissue specimens and urine for either serotonin (5-hydroxytryptamine) or 5-hydroxyindoleacetic acid (5-HIAA).



Fig. 1 (Honrubia, Davis, Moore, and Elliott). Note fullness of both lower eyelids, greater on patient's right.

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## Case report

*Case* 1—This 74-year-old white woman was first seen in the Vanderbilt University Hospital Eye Clinic on April 17, 1968, complaining of diplopia of approximately 13 months' duration and a mass under her right eye of four months' duration.

Four years earlier, the patient had a "gastric ulcer" which presented with massive melena and responded to medical therapy. Over the past 18 months, she had a 60-pound weight loss. Seven months before being seen, she had a "malignant tumor" removed from her left neck, with subsequent cobalt therapy to the operative field. Shortly thereafter, she had some "scalp masses" excised. These two specimens were interpreted initially as "adenocarcinoma of sweat glands."

Visual acuity was RE: 20/30 and LE: 20/25-2. Tension was 17.3 mm Hg (Schiøtz) in each eye. Bilateral firm nodular masses were palpated at the inferior orbital rims which extended back into the orbits. The right mass was more prominent (Fig. 1). The masses moved with movement of the globes. Eyelids, conjunctiva, cornea, anterior chamber, iris, and pupils were within normal limits in both eyes. Each lens had a mild nuclear and cortical opacities. Ophthalmoscopy revealed two small, healed chorioretinitic scars in the periphery of the right eye at 3 and 5 o'clock. Limited abduction and a hypertrophia were present in the right eye (Fig. 2). The patient had diplopia in all fields of gaze. Exophthalmometer readings were 19 mm bilaterally. Orbital x-ray studies, including optic foramina

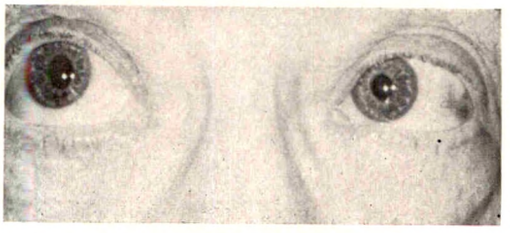


Fig. 2 (Honrubia, Davis, Moore, and Elliott). Patient with bilateral orbital metastases. On right conjugate gaze there is a right hypertropia and limitation of abduction.



Fig. 3 (Honrubia, Davis, Moore, and Elliott). Biopsy of right orbital mass. The tumor is highly cellular with connective tissue septa and capsule (hematoxylin-eosin, ×10).

views, were unrevealing. The orbital masses were thought to represent metastases from the same tumor which had involved the scalp and neck.

The patient was admitted for biopsy of the orbital masses. A general physical examination revealed a small, movable, firm nodule in the posterior triangle of the right neck and small mass in the left breast. A biopsy of the right orbital mass and a needle biopsy of the left breast mass revealed similar tumors. Microscopically, the specimens were composed of nests of cells with pale, eosinophilic cytoplasm and uniform nuclei. The nuclear chromatin was clumped and dispersed. The most peripheral cells in the nest had darker, more eosinophilic cytoplasm and the nuclei in this peripheral layer were oriented away from the basement membrane (Figs. 3 and 4). The peripheral cells were argentaffin-positive as indicated by reduction of silver leaving brownish-black deposits in the cytoplasm (Fig. 5). The diagnosis was argentaffinoma (malignant carcinoid). Comparisons were then made with the scalp and left neck specimens obtained in 1967. All were thought to represent the same tumor type, argentaffinoma.

With this diagnosis, further studies were undertaken to ascertain if there was involvement of other systems. Chest films, metastatic bone series, upper gastrointestinal series, small bowel series, barium enema, liver scan, and liver function studies were all non-revealing.

Although a vague history of recent episodes of flushing was obtained, the patient had never experienced the dramatic attacks of classic carcinoid syndrome. Therefore, a provocative epinephrine test was done. Four minutes after intravenous injection of 0.5 μg of epinephrine the patient noted a warm feeling over her face and a facial flush could be observed. With a 4.0 μg dose, a generalized flush was noted. There was no marked change in the patient's blood pressure or pulse and she had no asthmatic symptoms. The results of the test were felt to be abnormal, but of a mild degree.

The 24-hour urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) ranged from 9.2 to 12.6 mg. Although not extremely high, these values were definitely increased. The nodule in the right posterior triangle of the neck was biopsied on August 8, 1968, and was the same type as the other specimens —argentaffinoma. An assay for serotonin was made on a portion of the biopsied neck mass and showed a very high value of serotonin, 1.4 mg/g of wet tissue. This further confirmed the diagnosis of argentaffinoma.

When last seen in the Eye Clinic on July 28, 1970,

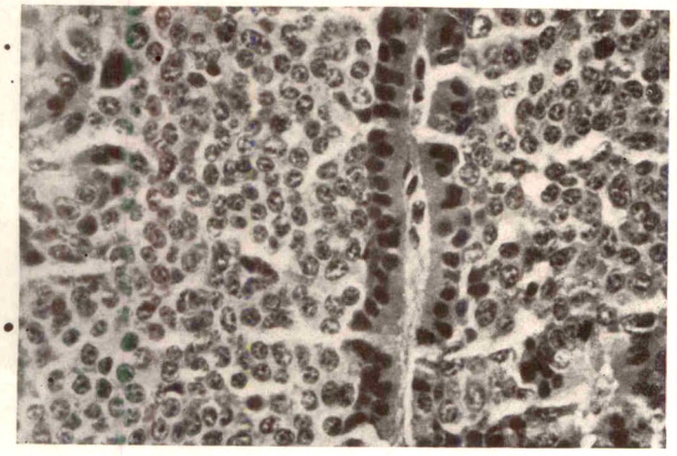


Fig. 4 (Honrubia, Davis, Moore, and Elliott). Photomicrograph of right orbital mass. The tumor is composed of two cell types. The major portion of the cells have a pale cytoplasm, uniform nucleus and dispersed chromatin. Other cells forming the boundary of cell nests have a darker cytoplasm with a prominent nucleus. This latter type of cell shows a palisading pattern with the nucleus oriented away from the basement membrane (hematoxylin-eosin, ×400).

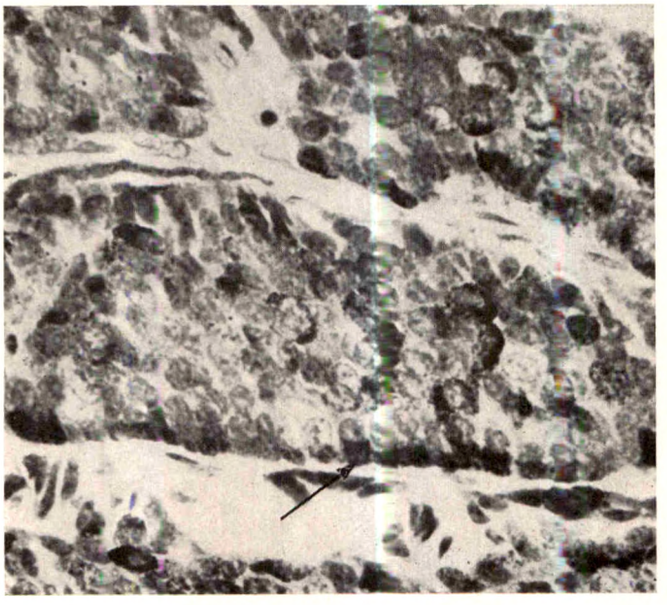


Fig. 5 (Honrubia, Davis, Moore, and Elliott). Photomicrograph of right orbital mass. Cytoplasm of cells exhibit dark granules indicating a positive argentaffin reaction after silver staining (arrow) (Fontana-Masson, ×400).

the patient's ocular examination was essentially unchanged. She was experiencing flushes every day and she had additional masses in the right orbit superiorly, the right triceps area, and the left axillary area.

## Comment

One case of unilateral orbital metastasis of carcinoid has been reported.[3] However, in the patient reported here, the orbital metastases were bilateral. Although the primary site of the carcinoid tumor was not found, the diagnosis was made from the clinical symptomatology and the histopathologic study of biopsies taken from the orbit, neck, and breast. This was further substantiated by: (1) the positive argentaffin reaction in the orbital tumor, (2) the high levels (9.2-12.6 mg/24 hours) of 5-HIAA in the urine (normal, 1-9 mg), (3) the high level of serotonin in the biopsy specimen from the nodule in the posterior triangle of the neck (usual levels in gastrointestinal carcinoid range from 10 to 60 μg/g wet tissue).

From the literature it must be concluded that the incidence of metastatic orbital carcinoma is quite uncommon. When orbital metastasis does occur, the site of the primary tumor is usually the breast or lung.[4] It has been estimated that metastatic carcinoma to the orbit is only one-fifth as frequent as metastatic involvement of the globe.[5] Hart[6] reviewed a total of 133 cases of carcinoma metastatic to the eye and orbit in the registry of the Armed Forces Institute of Pathology up to 1958; he found orbital involvement in only 14 cases. Other authors reporting large series of orbital tumors also show that metastatic carcinoma to the orbit is infrequent.[7-9]

Bilaterality in metastatic carcinoma to the orbit would appear to be an exceedingly rare event. Haye[10] states that only four cases have been described. By constrast, bilateral orbital metastases of tumors other than carcinoma is more common; Albert, Rubenstein, and Scheie[11] found that 56% of children with orbital metastases from neuroblastoma had bilateral involvement. Cases of intraocular metastases from all types of tumors are seen more frequently and 20–25% are bilateral.[12]

We agree with other authors who have suggested that the reason for the low reported incidence of metastatic orbital carcinoma is that patients with metastatic disease are rarely treated in eye hospitals and orbital tissues are infrequently submitted for pathologic examination.[4]

## Summary

A case of bilateral orbital metastases from a carcinoid tumor is reported. The ophthalmic findings prompted biopsy and histopathologic studies which resulted in the diagnosis of argentaffinoma, which was further confirmed by a positive argentaffin reaction in the orbital tumor, the elevated level of 5-HIAA in the urine, and the high concentration of serotonin present in the tumor. Reevaluation of previously biopsied masses also revealed the argentaffinoma pattern. Following pathologic diagnosis, the patient later developed the classic syndrome.



## Acknowledgments

The serotonin assay of tumor tissue and 5-HIAA level in the urine were performed in the laboratory of John A. Oates, M.D., Professor of Pharmacology and Medicine, Vanderbilt University Medical School. We thank John L. Shapiro, M.D., Professor of Pathology, and Barton McSwain, M.D., Professor of Surgery, Vanderbilt University Medical Center, who reviewed the histopathologic sections.


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# AXIAL TOMOGRAPHY OF OPTIC CANALS IN DIAGNOSIS OF CHILDREN'S EYE AND OPTIC NERVE DEFECTS

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Axial tomography of the optic canals is the only method by which the entire length of both optic canals can be visualized on one x-ray film. Both sides can be viewed simultaneously to compare minor changes and demonstrate pathology affecting only one part of the optic canal. This method was recently standardized by examination of 50 normal children.[1]

We have used axial tomography for diagnosis of several congenital conditions, tumors and injuries to the globe and optic pathways.

## MATERIAL AND METHODS

Forty-five children between the ages of two months and 17 years were examined by axial tomography of the optic canals. Patients selected for the study had one of the following conditions: a tumor affecting the optic nerve, a congenital eye disease possibly connected with changes in the optic nerves, or an injury of the orbit which might involve the optic canal.

We followed the method of axial hypocycloidal tomography as suggested by Dilenge, Metzger, and Simon,[2] and Harwood-Nash.[1] The child was placed supine on a padded box with the head over one edge, the neck extended maximally (Fig. 1). In each case, six hypocycloidal tomograms were taken about the optic canals in the axial plane to include the anterior and posterior clinoids,

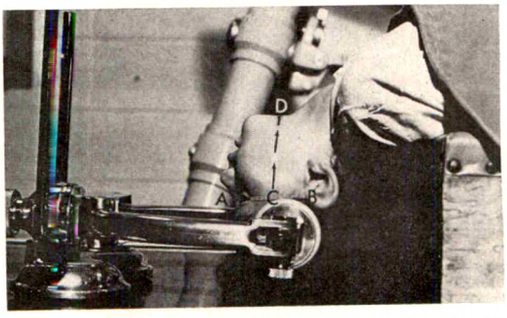



Fig. 1 (Merin, Harwood-Nash, and Crawford). Position of child for axial tomography of the optic canals. Line A-B (from the outer canthus of the eye to the ear) is parallel to the tabletop. A perpendicular line to C (the middle of A-B) fixes the point D, on the sagittal line, on which the tube is focused.

the tuberculum sellae, and the body of the sphenoid. Figure 2 is an axial tomogram of a normal optic canal.

The optic canals were stated to be normal if they were identical to one another, normal in shape, and the transverse diameter at the mid-portion was within the normal values

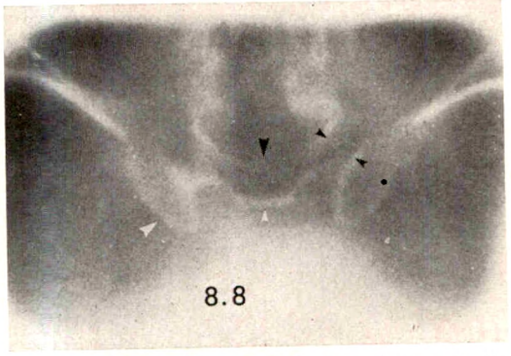



Fig. 2 (Merin, Harwood-Nash, and Crawford). Axial tomogram of a normal optic canal at its mid-level (in this case, 8.8 cm from the vertex of the head). The structures which can be seen are the optic canals (left canal indicated by small black arrows), the sphenoid body (indicated by large black arrow), tuberculum sellae (indicated by small white arrow), anterior clinoid processes (right process indicated by large white arrow).

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(Table 1). Canals were considered abnormal if the diameter was larger or smaller than the above values, if there was a segmental narrowing or widening in one or both canals, if a canal was occluded, or if a fracture was seen.

## Results

The results are shown in Table 2.

We present here a brief description of the findings for each diagnosis and add some illustrative case reports.

### Glioma

Enlargement of one optic canal was found in all seven patients with optic nerve glioma. In five, both canals were affected. In all cases, subsequent neurologic and radiologic examinations and, later, surgery and biopsy confirmed the diagnosis.

#### Case report

*Case* 5—A four-and-one-half-year-old girl had a right exotropia for two years. Visual acuity was limited to finger counting. The optic disk was pale. The left eye appeared normal. Routine roentgenograms showed the right optic foramen enlarged and the left normal (Fig. 3). Axial tomograms showed the right optic canal enlarged to 10 mm in diameter and the funnel-shaped left optic canal 6 mm in diameter (Fig. 4). A preoperative diagnosis of bilateral glioma of the optic nerves was made. At operation the right optic nerve was five times its normal diameter and the tumor extended back into the chiasm and forward into the left optic canal. No radical excision was performed and the patient was sent for radiologic treatment.

### Craniopharyngioma

Six cases were examined. All showed scalloping of the sphenoid, clawing of the medial side of both anterior clinoids, and funnelling of the intracranial portion of one or both optic canals.

#### Case report

*Case* 12—A nine-year-old boy had been suffering from growth retardation for several years. He discovered accidentally that he could not see with his right eye. The right eye did not perceive light, owing to total optic atrophy. The left eye had visual acuity of 20/40, pallor of the disk and temporal hemianopsia. Roentgenograms showed normal optic foramina, but axial tomograms showed an invasion of both optic canals by tumor (Fig. 5). A subtotal excision of a craniopharyngioma was performed.

TABLE 1

Transverse diameter* of the mid-portion of normal optic canals in children

| Age in Years | Transverse Diameter of Optic Canal | |
|---|---|---|
| | Minimum | Maximum |
| Under 1 | 3 mm | 5 mm |
| 1 to 3 | 4 mm | 5 mm |
| Over 3 | 4 mm | 7 mm |

* Measured on roentgenograms, and so about one-third larger than the actual size.

### Other tumors

One patient (Case 13) had neuroblastoma and meastasis to the left orbit. Tomograms of the orbit showed destruction of the lateral wall, but axial tomograms of the optic canals showed that the canal was not involved.

### Anophthalmus

Five cases of anophthalmus were examined. Three were congenital, and on palpation of the socket under anesthesia no vestigial eye was found. The optic canal on the affected side was narrow in all three and occluded in two of them.

#### Case reports

*Case* 14—A two-and-one-half-year-old boy was examined because of bilateral congenital anophthalmus, had palpebral fissures measuring 15 mm each. Roentgenographic examination of the optic foramina showed them to be slightly flat in the vertical diameter (Fig. 6). Axial tomograms showed the optic canals to be small and occluded (Fig. 7).

Clinical anophthalmus had been diagnosed in one patient (Case 17), but palpation under anesthesia revealed a small pea-size eye. The axial tomograms showed normal optic canals.

*Case* 18—In this seven-year-old girl with acquired anophthalmus, the optic canals were normal. Because of retinoblastoma she had her right eye removed at the age of eight weeks and her left eye at the age of two-and-one-half years. After the enucleation, each socket was treated by a plastic ball and conformer. Axial tomograms showed normal optic canals.

## TABLE 2

TOMOGRAPHY OF THE OPTIC CANALS IN CHILDREN

| Case No. and Age (in years) | Clinical Diagnosis | Optic Canals: Diameter (in mm) | | Remarks |
|---|---|---|---|---|
| | | Right | Left | |
| 1–11 | Glioma of both optic nerves | 5.5 | 5.5 | Optic foramina normal, funnelling of proximal part of both canals |
| 2–10 | Glioma of both optic nerves | 7.0 | 8.0 | Enlarged |
| 3– 6 | Glioma of left optic nerve | 5.0 | 8.0 | Enlarged |
| 4– 2 | Glioma of both optic nerves | 8.0 | 9.5 | Enlarged |
| 5– 4½ | Glioma of both optic nerves | 10.0 | 6.0 | Figures 3 and 4 |
| 6– 7 | Glioma of right optic nerve | 8.0 | 6.0 | |
| 7– 2 | Glioma of both optic nerves | 7.0 | 8.0 | |
| 8–15 | Craniopharyngioma | 6.0 | 6.0 | See text |
| 9–15 | Craniopharyngioma | 5.5 | 6.0 | See text |
| 10–14 | Craniopharyngioma | 6.0 | 6.0 | See text |
| 11–13 | Craniopharyngioma | 7.0 | 7.0 | See text |
| 12– 9 | Craniopharyngioma | 6.0 | 5.0 | Figure 5 |
| 13– 2½ | Neuroblastoma with metastasis to the left orbit | 5.0 | 5.5 | Normal |
| 14– 2½ | Bilateral congenital anophthalmus | 3.5 | 0 | Small on right side, blind pouch on left |
| 15– 3 | Right congenital anophthalmus | 0 | 4.0 | Blind pouch on right side |
| 16– 1½ | Left congenital anophthalmus (Weyers-Thier syndrome) | 6.0 | 3.5 | Small on left |
| 17– 6 | Left congenital extreme microphthalmus (to the extent of anophthalmus) | 4.5 | 4.5 | Normal |
| 18– 7 | Bilateral anophthalmus, postenucleation | 5.0 | 5.0 | Normal canals |
| 19– 1 | Bilateral congenital microphthalmus and cataract | 7.5 | 7.0 | Large, bilateral |
| 20– 4 | Right congenital microphthalmus and cataract | 5.0 | 5.0 | Normal |
| 21– 4½ | Bilateral microphthalmus and uveal coloboma | 5.0 | 4.0 | Normal |
| 22– 6 | Bilateral congenital microphthalmus uveal coloboma | 4.5 | 5.0 | Normal |
| 23– 3 | Bilateral hypoplastic disk | 3.5 | 3.0 | Small, bilateral |
| 24– 7 | Right hypoplastic disk | 4.0 | 6.0 | Small, right |
| 25– 6 | Left hypoplastic disk | 6.0 | 3.5 | Small, left |
| 26– 9 | Right negalopapilla | 6.0 | 6.0 | Normal |
| 27–17 | Coloboma of right optic disk | 6.0 | 6.0 | Normal |
| 28– 3½ | Bilateral congenital optic atrophy | 3.0 | 3.0 | Small, bilateral |
| 29– 2 | Right congenital optic atrophy | 4.5 | 5.5 | Slightly small, right |
| 30–12 | Left post-traumatic optic atrophy | 6.0 | 5.5 | Normal |
| 31– 1 | Leber's amaurosis congenita | 5.5 | 5.5 | Normal |
| 32–14 | Leber's amaurosis congenita | 4.0 | 4.0 | Lower limits of normalcy |
| 33– 2 | Right microphthalmus with persistent hyperplastic primary vitreous | 5.0 | 4.5 | Normal |
| 34– 2 | Left microphthalmus with persistent hyperplastic primary vitreous | 5.0 | 4.5 | Normal |
| 35–16 | Congenital nystagmus with hyperopia | 6.0 | 6.0 | Normal |
| 36 | Congenital nystagmus with hyperopia | 5.0 | 5.0 | Normal |
| 37–3½ | Congenital nystagmus with hyperopia | 4.5 | 4.5 | Normal |
| 38–10 | Congenital nystagmus with hyperopia | 4.0 | 4.0 | Slightly small |
| 39– 1 | Congenital glaucoma | 5.0 | 4.0 | Normal |
| 40– 2 | Congenital toxoplasmosis | 3.0 | 3.0 | Normal |
| 41–10 | Right high myopia | 5.5 | 5.5 | Normal |
| 42– 1 | High hyperopia | 6.0 | 6.0 | Normal |
| 43– 9 | Trauma | 5.5 | 5.5 | Broken bone |
| 44–12 | Trauma | 5.0 | 5.0 | Broken bone blocking optic canal |
| 45– 7 | Trauma | 6.0 | 6.0 | Broken bone blocking optic canal |

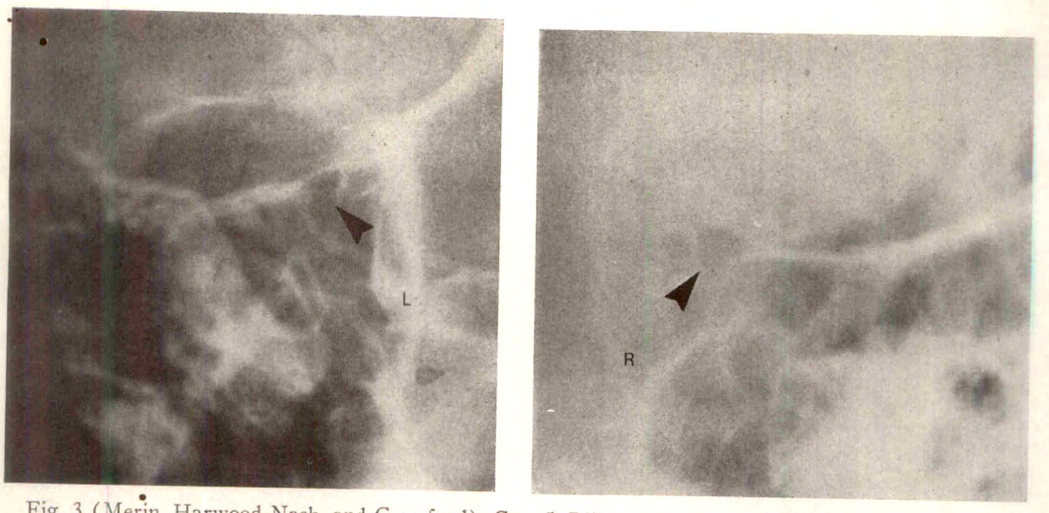



Fig. 3 (Merin, Harwood-Nash, and Crawford). Case 5. Bilateral glioma of the optic nerves and chiasm. Right: Plain roentgenograms showing right optic foramen enlarged. Left: Left optic foramen is normal.

### Congenital microphthalmus

Four cases were examined, two had an associated congenital cataract and two had an associated uveal coloboma. In three, the optic canals were within normal limits and in the following case (Case 19) they were unusually large.

#### Case report

*Case* 19—This one-year-old boy, blind since birth, had bilateral microphthalmus, the cornea measuring only 8 mm in diameter. Bilateral mature congenital cataracts did not allow us to visualize the fundus. The child and his mother showed some signs of abnormal development of the first two branchial arches and she, too, had a congenital microphthalmus with cataract of her right eye, which was blind since birth. The boy's axial tomograms showed unusually wide optic canals (Fig. 8).

### Hypoplasia of optic nerves

Congenital hypoplastic disk was diagnosed in three cases. In all three, axial tomograms of the optic canals showed them to be abnormally narrow on the affected side, for example, in Case 25.

#### Case report

*Case* 25—This six-year-old boy had been examined for exotropia of his left eye since infancy. The right eye was found normal, its visual acuity

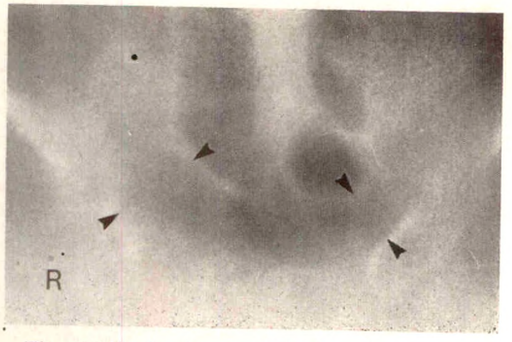



Fig. 4 (Merin, Harwood-Nash, and Crawford). Case 5. Axial tomogram showing wide optic canal on right (R), normal mid-portion of left optic canal (black arrows), and a funnel widening of the posterior part of the left optic canal.

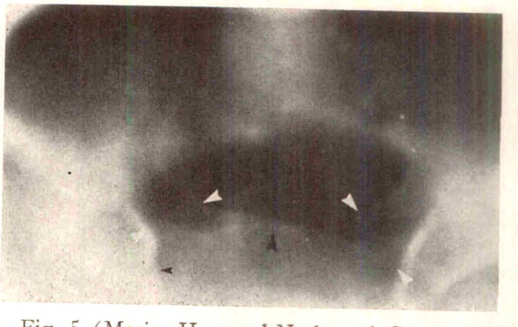


Fig. 5 (Merin, Harwood-Nash, and Crawford). Case 12. Craniopharyngioma with bilateral extension into the optic canals. Axial tomogram showing clawing of anterior clinoid process (small black arrow). The posterior part of each canal is widened (white arrows). The larger black arrow indicates scalloping of the sphenoid.

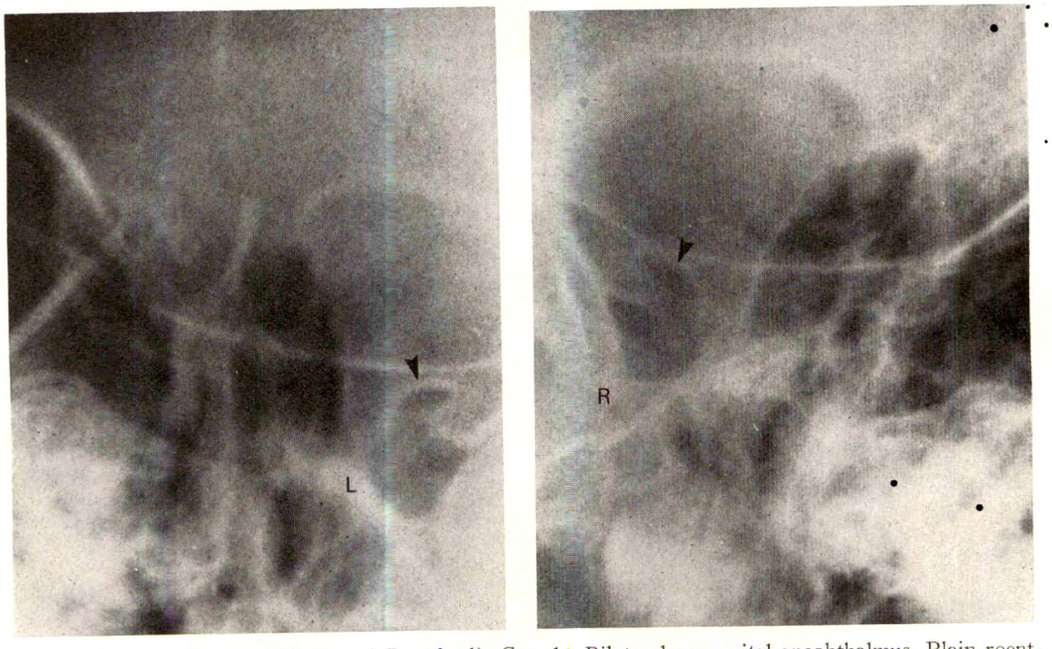



Fig. 6 (Merin, Harwood-Nash, and Crawford). Case 14. Bilateral congenital anophthalmus. Plain roentgenograms showing optic foramina slightly flattened in the vertical diameter and elongated in the horizontal diameter.

being 20/20 (with −1.0 sph. ⊃ −0.50 cyl. ax. 188°). The left eye had constant exotropia of 15Δ. Visual acuity was 20/50 (with −0.50 sph. ⊃ −0.50 cyl. ax. 90°). The pupils were normal and their direct and consensual response to light was normal. The fundus showed a small hypoplastic disk (Fig. 9). Roentgenograms showed normal and equal optic foramina. Axial tomograms of the optic canals showed a narrow optic canal on the left side (Fig. 10).

### Megalopapilla

One case of megalopapilla showed normal optic canals.

#### Case report

*Case 26*—This nine-year-old boy was referred to us after routine eye examination revealed an abnormal right optic disk. The visual acuity was 20/20 in

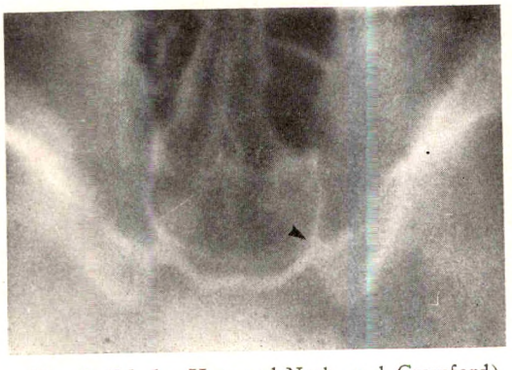


Fig. 7 (Merin, Harwood-Nash, and Crawford). Case 14. Axial tomogram showing occluded midportion of left optic canal (arrow) and narrowed right optic canal.



Fig. 8 (Merin, Harwood-Nash, and Crawford). Case 19. Bilateral microphthalmus. Axial tomogram showing large optic canals (right, 7.5 mm; left 7.0 mm).




Fig. 9 (Merin, Harwood-Nash, and Crawford). Case 25. The right (A) and left (B) fundus of a patient with a left hypoplastic disk. The white mark at the bottom of B is a light reflex.

each eye. The right optic disk was enlarged by about 50% (Fig. 11), and had some temporal pallor. Intraocular pressure was normal. The blind spot was enlarged with a partial supratemporal quadrantanopsia. Axial tomograms showed normal optic canals. Neurologic examinations were negative.

### Coloboma of optic disk

One case of coloboma of optic disk showed normal optic canals.

### Optic atrophy

Three patients with optic atrophy were examined. In one of the two congenital cases, the optic canals were small; in the other they were within normal limits though smaller on the affected side. In Case 30, optic atrophy resulted from injury in the first year of life. At 12 years of age the optic canals appeared normal and practically equal.

### Miscellaneous congenital conditions

The optic canals were normal in two patients with Leber's congenital amaurosis, two with hyperplastic persistent primary vitreous with microphthalmia, four with congenital nystagmus and hyperopia, and one each with congenital glaucoma, congenital toxoplasmosis, congenital high myopia, and congenital high hyperopia.

### Trauma

Axial tomograms showed fractures of the wall of the optic canal in three patients with trauma.

### Case report

*Case* 44—A 12-year-old girl, brought to the emergency department after a snowmobile accident, had no light perception in either eye. The right globe was ruptured and the central retinal artery on the left was occluded. Tomograms of the optic canals showed a fragment of bone penetrating into the right optic canal (Fig. 12).

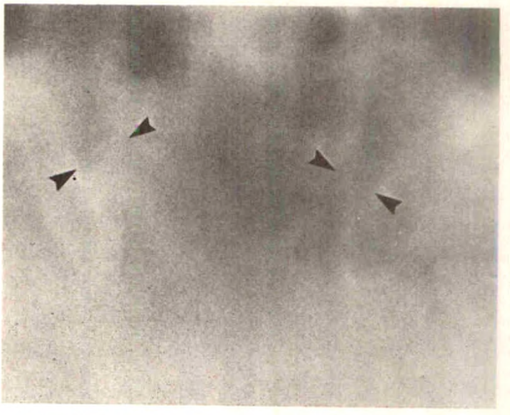


Fig. 10 (Merin, Harwood-Nash, and Crawford). Case 25. Axial tomogram showing left optic canal (L) narrower than the right (patient 25).

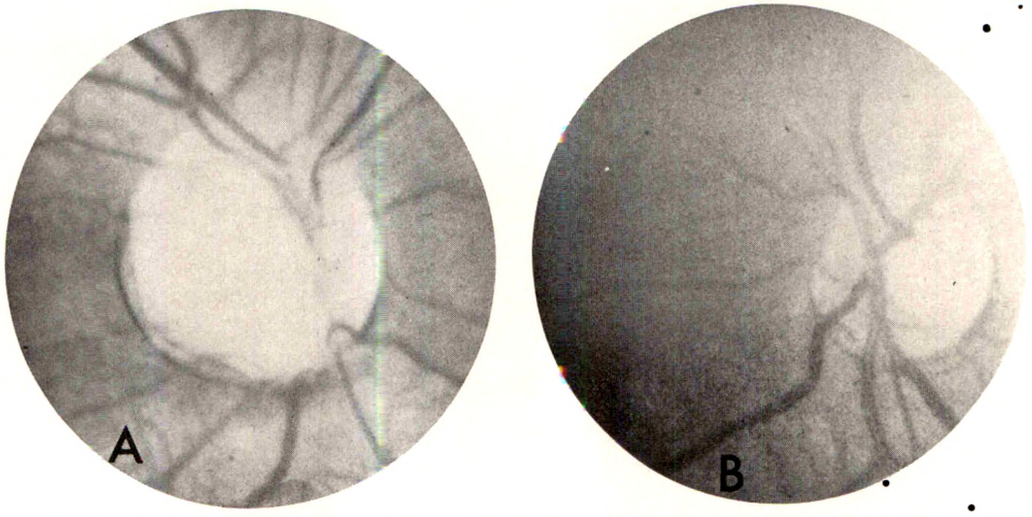



Fig. 11 (Merin, Harwood-Nash, and Crawford). Case 26. Right megalopapilla. The right disk (A) is enlarged, the left disk (B), normal.

## Discussion

Axial tomography of the optic canals is simple to perform in children. The necessity for hyperextension of the neck might make this type of tomography difficult to perform in adults.

The widening of an optic foramen seen on a plain roentgenogram is considered pathognomonic or glioma of the optic canal. A tumor, however, may be in the canal behind the foramen and hence only demonstrable by tomography. In Case 1 the foramina were normal but the axial tomograms showed an intrusion of both optic canals by the tumor from the direction of the chiasm. In Case 5, when plain roentgenograms showed only an abnormal right optic foramen, the axial tomograms showed that the left optic canal was involved as well.

Craniopharyngioma can readily be diagnosed by axial tomography. The clawing of the anterior clinoids, the scalloping of the body of the sphenoid and the proximal funnelling of the optic canals found concurrently in all cases were not seen in any other pathologic condition.

Anophthalmus, congenital or surgical, in a young child retards development of the orbit and the optic canal on the affected side.[3] The degree of this retardation depends on the age of the child and it is much less if an implant is inserted.[4] In all cases of microphthalmus the optic canals were normal; in all cases of anophthalmus they were abnormal. The only case diagnosed as congenital anophthalmus in which axial tomography showed no abnormality of the optic canals proved later to be congenital microphthalmus. Thus axial tomography may distinguish between true anophthalmus and microphthalmus.

Controversy exists about the value of plain roentgenograms of the optic foramina

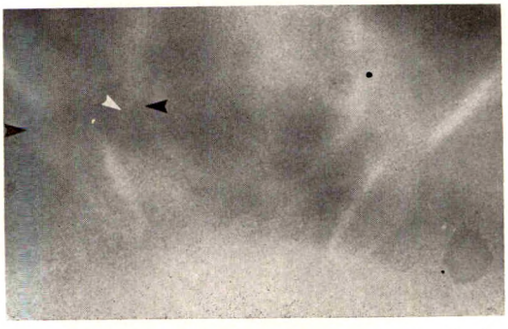


Fig. 12 (Merin, Harwood-Nash, and Crawford). Case 44. Trauma. Axial tomogram showing fracture of medial and lateral walls of right optic canal and across base of right clinoid process (black arrows) with a fragment of bone penetrating the canal (white arrow).

in diagnosis of hypoplasia of optic nerve, a condition in which the optic nerve contains fewer nerve fibers.[5] Several authors found the optic foramen small on the affected side,[6,9] others[10] found it normal. Recently, in two large series[11,12] plain roentgenograms were reported to be of no value. Axial tomography of the optic canal, however, clearly demonstrated narrowing of the canal in all three cases we examined. This narrowing may be a pathognomonic sign of hypoplasia of the optic nerve.

In a single case of the rare megalopapilla (Case 26) our findings of a normal canal confirm those of Franceschetti and Bock.[13]

Small optic canals were demonstrated in two cases of congenital optic atrophy. In one case of early acquired optic atrophy (Case 30), tomograms were normal. More cases will have to be examined in order to find out if this difference is always found.

A fracture of the optic canal is often difficult to demonstrate in plain x-ray films, but shows up clearly in axial tomograms.

Potter and Trokel[14-15] recently advised the use of anterior-posterior (A-P) hypocycloidal tomography of the optic canals and proved its superiority over plain roentgenograms of the optic foramina. However, A-P tomography, unlike axial tomography, does not show the whole length of the optic canal on one film and can be inaccurate when the angle of tomography does not correspond to the angle of the optic canal. Whereas A-P tomography is done always at a fixed angle, the average angle of the optic canal to the sagittal line is 36[16] or 37 degrees[14,15] with frequent individual variations which are greater and more common in children than in adults.[1]

## Summary

Hypocycloidal axial tomography of the optic canals was used to examine 45 children with various congenital and acquired diseases of the globe and optic nerve. It provided accurate assessment of unilateral or bilateral involvement in cases of glioma, craniopharyngioma, congenital anophthalmus, congenital optic atrophy, and congenital hypoplasia of the optic nerve; showed fracture in the wall of the optic canal in cases of injury; and revealed normal optic canals in cases of microphthalmus, coloboma of optic disk, Leber's congenital amaurosis, congenital nystagmus, congenital glaucoma, congenital toxoplasmosis, high myopia, and high hyperopia.

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# SACCADIC VELOCITIES IN INFANTS AND CHILDREN

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Previous investigations in adults[1,2] indicate that abnormal recovery saccades of optokinetic nystagmus are elicited in lateral rectus muscle palsy. The antagonist medial rectus performed the recovery saccade normally. The value of studying ocular saccades in other neurologic diseases has been pointed out.[3,4] Voluntary saccadic movements are easily elicited in adults, and less easily, these command movements can also be obtained in young children. Saccades generated by optokinetic nystagmus (OKN) are reflex saccades; these have the same characteristics as voluntary saccades, but can be easily elicited in children.

It was the purpose of this study to determine to what extent the reflex saccades of optokinetic nystagmus (OKN) may be of diagnostic value in infants and young children.

## MATERIALS AND METHODS

Seven infants with ocular motility problems were tested. The child was seated comfortably on his mother's lap at the center of a drum 0.85 meter in height and 0.75 meter in diameter (Fig. 1). Vertical black stripes, 12 mm wide, alternating with 36 mm vertical white stripes, covered the inside surface of the drum. The speed of rotation was 60 degrees per second, which resulted in eight black and eight white stripes passing a given point in one second. The drum could be rotated in either direction. Each eye was studied separately as the drum was rotated first in one direction and then reversed.

Eye movements were recorded by electrooculography (EOG), as previously described.[2] Miniature skin electrodes (Beckman) were placed on the medial canthus and lateral canthus and the indifferent electrode centrally over the brow (Fig. 2).



Fig. 1 (Metz, Scott, and O'Meara). Infant on mother's lap inside large drum used to generate optokinetic nystagmus.

Within several minutes, even in a difficult child, one can get an adequate record of the eye movements. The tracing was considered valid when three patterns of following movements—recovery (saccadic) movements were noted in a three-second interval.

Optokinetic nystagmus was recorded by electrooculography on cooperative adults to establish both the normal pattern and the

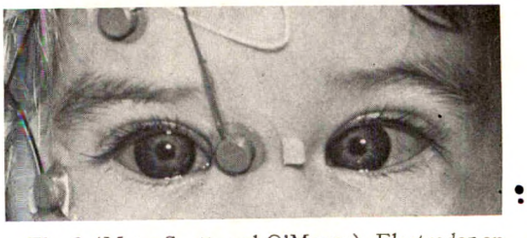


Fig. 2 (Metz, Scott, and O'Meara). Electrodes on medial and lateral canthi and centrally above the brow on infant.

From the Smith-Kettlewell Institute of Visual Sciences, San Francisco. This investigation was supported by Public Health Service Research Program Project Grant EY 00299 and Office of Naval Research contract Nonr 14-70-C0141.

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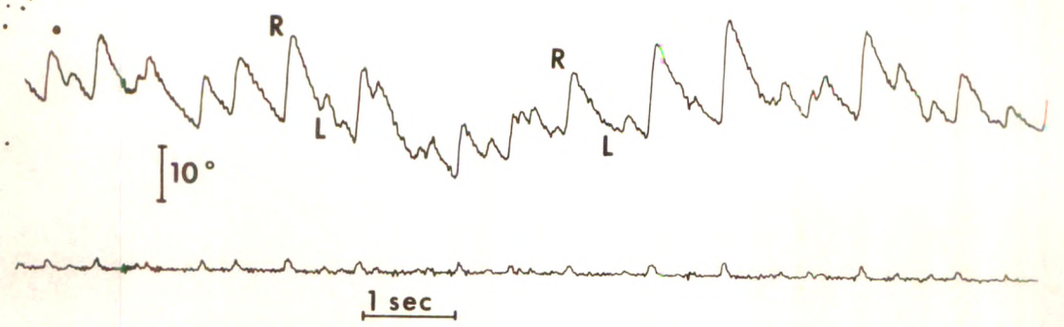



Fig. 3 (Metz, Scott, and O'Meara). EOG, left eye. Upper trace: Eye position and movement. Lower trace: Velocity. Movements generated to optokinetic nystagmus, drum rotated right (R) to left (L). Saccades to right are normally rapid suggesting normal medial rectus function.

pattern produced by a paretic muscle. Figure 3 demonstrates normal optokinetic nystagmus with a slow following and sharp recovery phase. A healthy medial rectus was responsible for the normal saccades obtained. Figure 4 displays abnormal optokinetic nystagmus as produced by a paretic lateral rectus muscle. The following and recovery movements are both slow. The saccades of optokinetic nystagmus produced by a normal and palsied muscle are easily differentiated by their different velocities.

## Case reports

*Case* 1—Moebius syndrome. This nine-month-old girl had had esotropia since birth (Fig. 5). Bilateral facial paralysis was present. Development was otherwise normal.

A V-pattern esotropia was present, measuring 80 prism diopters in downgaze, 60 prism diopters in primary gaze and 45 prism diopters in upgaze. Abduction did not bring either eye quite to the midline. Upward and downward gaze were mildly limited in each eye. Ophthalmoscopic examination was normal. In tests of this child, Figures 6 and 7 (upper trace) display normal recovery saccadic movements generated by the medial rectus. Figures 6 and 7 (lower trace) show recovery movements generated by the lateral rectus.

*Interpretation*—Abduction saccades bilaterally are slow and rolling and do not have normal saccadic velocity. These abnormal saccadic movements are similar to those seen in adults with known lateral rectus palsy. Normal horizontal saccadic movements have a velocity of above 250 degrees per second. These reflex saccades are about 50 degrees per second and indicate lateral rectus palsy in each eye. The EOG tracing resembles that of the adult sixth-nerve palsy with slow abduction saccades (Fig. 4), and shows that muscle paresis can be demonstrated in infants using this technique. When drum rotation is reversed, the direction of nystagmus is reversed. The medial rectus now functions as the agonist muscle for recovery movements, producing normal appearing optokinetic saccades. When the agonist muscle is normal, the saccadic velocity resulting from contraction of that muscle can serve as a control.

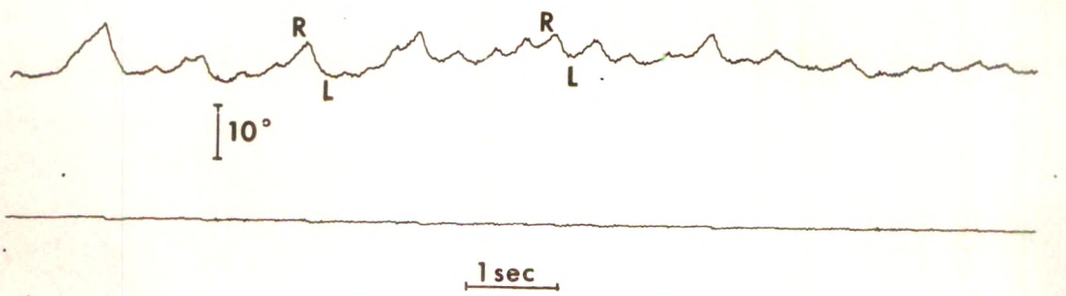



Fig. 4 (Metz, Scott, and O'Meara). EOG, left eye. Upper trace: Eye position and movement. Lower trace: Velocity. Movements generated by optokinetic nystagmus, drum rotated left (L) to right (R). Saccades to left are slow suggesting paresis of the lateral rectus muscle.

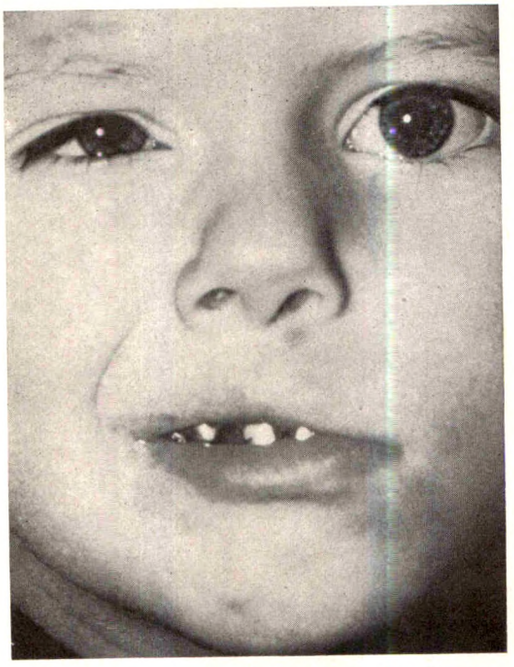


Fig. 5 (Metz, Scott, and O'Meara). Moebius syndrome. Bilateral sixth and seventh nerve palsy with esotropia.

*Case 2*—Limitation of abduction. This 21-month-old boy had been normal until five weeks of age. Following an automobile accident, he developed a subdural hematoma, hydrocephalus, and esotropia. A shunt procedure was performed to relieve the hydrocephalus. His mental and motor development were estimated at about the nine-month level. Examination revealed an alternating esotropia of 75 prism diopters (Fig. 8). Abduction was limited to almost 10 degrees lateral to midline in each eye and was not improved by patching. Vertical movements were full. Ophthalmoscopic examination was normal bilaterally. OKN saccades were observed and recorded in the area where movements were possible (i.e., nasal to the midline).

*Interpretation*—In Figures 9 and 10, the upper traces demonstrate recovery saccades generated by the medial recti and the lower traces, saccades generated by the lateral recti. In both instances, saccades are rapid and sharp. They suggest normal function of each lateral rectus muscle in the presence of diminished voluntary abduction bilaterally.

At surgery, the forced duction test revealed significant restriction to abduction in each eye. Bimedial rectus recessions of 5 mm and bilateral rectus resections of 7 mm were performed. Two months following surgery, the eyes were straight and abduction was full in each eye.

The status of the lateral recti in this patient was not certain prior to saccadic testing. History suggested lateral rectus paresis resulting from trauma. The marked esotropia persisted since the injury and there may have been little or no recovery of the lateral recti. The rapid saccades generated by the lateral recti in each eye suggested normal function. The return of full abduction following surgery confirmed the absence of lateral rectus palsy. The forced duction test at surgery confirmed the presence of mechanical restriction to abduction bilaterally.

## Discussion

Ocular saccades, whether voluntary or induced reflexly by optokinetic nystagmus, provides a stress test for the oculomotor system. Comparison of normal saccades with saccades of patients with motility defects is a simple yet accurate way of uncovering paresis of an extraocular muscle.

The drum used to produce optokinetic

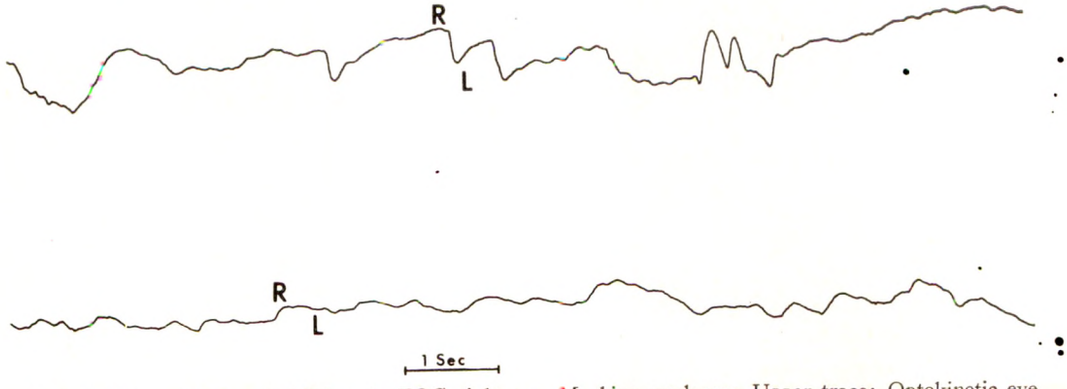



Fig. 6 (Metz, Scott, and O'Meara). EOG right eye, Moebius syndrome. Upper trace: Optokinetic eye movements, drum rotated left (L) to right (R). Recovery saccades to left are rapid. Lower trace: Optokinetic eye movements, drum rotated right (R) to left (L). Recovery saccades right are slow, suggesting paretic right lateral rectus muscle.

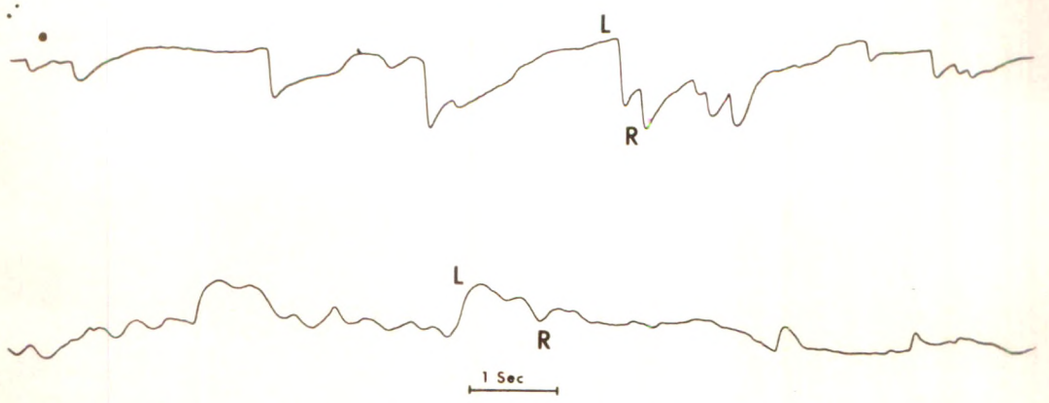



Fig. 7 (Metz, Scott, and O'Meara). EOG left eye, Moebius syndrome. Upper trace: Optokinetic eye movements, drum rotated right (R) to left (L). Recovery saccades to right are rapid. Lower trace: Optokinetic eye movements, drum rotated left (L) to right (R). Recovery saccades left are slow, suggesting paretic left lateral rectus muscle.

nystagmus should be large and encircle the patient to form a large field of moving stripes. This provides greater assurance that the child will be stimulated visually by the rotating stripes, wherever he looks. The stripes should be wide enough to be seen with reduced visual acuity. The object is to produce good OKN. Whatever speed of drum rotation, number of stripes in the visual field, or ratio of the size of the black and white stripes that does this, will be satisfactory.

Recording the eye movements of induced optokinetic nystagmus has several advantages over visual observation alone. A permanent record is acquired, the pattern of movement can be studied more completely at a later time and body and head movements need not be restricted nor the lids held apart to inspect the eyes. EOG equipment is often available at centers that perform electronystagmography.

The speed of a saccadic eye movement is not under voluntary control. A subject cannot purposely produce a slow saccade. The physician thus assumes control of the testing situation and the velocity of the saccadic eye movement is representative of the active force which can be generated by the agonist muscle.

It has been previously pointed out that resection of a paralytic extraocular muscle, even with recession of a contractured antagonist, cannot be expected to either maintain ocular alignment in the primary position or to increase the range of motility.[5] If the antagonist is not contractured or if it has been significantly recessed, it may be possible to provide greater range of motion by extraocular muscle transplantation surgery. It therefore becomes important to know about the mechanical forces in the orbit and the active forces capable of being generated by certain muscles. The former will be revealed by the forced duction test which can be done in infants while under anesthesia just prior to surgery. The active forces can be estimated in adults by use of the Scott active force test[5] and by ocular electromyography.[6] These tests cannot readily be done in infants or young children, so other objective recording techniques must be used.

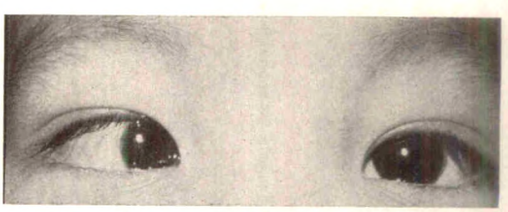


Fig. 8 (Metz, Scott, and O'Meara). Bilateral abduction limitation with large angle esotropia.

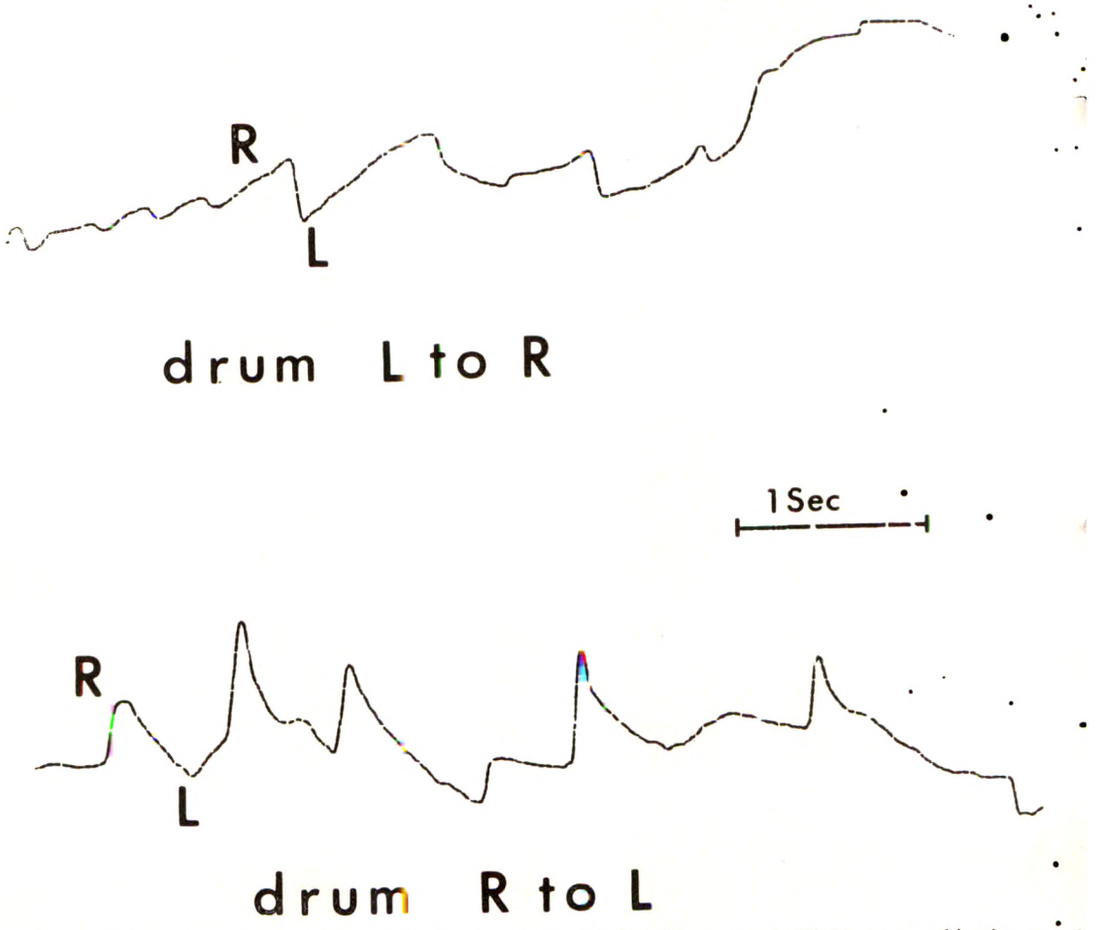



Fig. 9 (Metz, Scott, and O'Meara). EOG, abduction limitation. Upper trace: Right eye, optokinetic eye movements, drum rotated left (L) to right (R). Recovery saccades to the left are rapid. Lower trace: Left eye, optokinetic eye movements, drum rotated right (R) to left (L). Recovery saccades to the right are rapid. Normal medial recti in each eye.

When muscle surgery is performed without knowledge of the innervational status of the ocular muscles, the decision concerning which muscles to operate upon and the amount of surgery required is necessarily based on guess work. We believe the method of generating saccades with optokinetic nystagmus while recording eye movements with EOG can provide useful information to the ophthalmologist in diagnosis, prognosis, and surgical planning.

## Summary

Ocular saccades were generated in infants and children by optokinetic nystagmus. These movements were recorded by means of electrooculography.

A normal saccade was generated by a normal extraocular muscle while an abnormally slow saccade is produced by a paretic extraocular muscle. By comparing the saccade produced by a suspected paretic muscle with normal saccades, paresis can be detected in young patients. The test is useful for diagnosis, prognosis and surgical planning in infants and children with paralytic strabismus. In children, where there are limitations in doing the forced duction test and ocular electromyography, one can use electro-oculography and generate reflex saccades with opto-

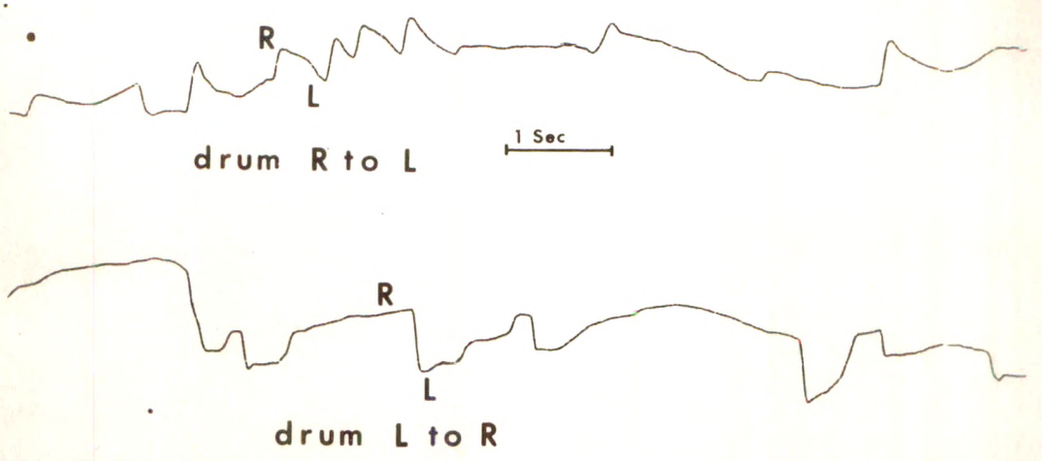



Fig. 10 (Metz, Scott, and O'Meara). EOG, abduction limitation. Upper trace: Right eye, optokinetic eye movements, drum rotated right (R) to left (L). Recovery saccades to right are rapid. Lower trace: Left eye, optokinetic eye movements, drum rotated left (L) to right (R). Recovery saccades to left are rapid. Normal lateral recti in each eye.

kinetic nystagmus in perplexing problems where paresis is suspected.

ACKNOWLEDGMENT

We thank Dr. Arthur Jampolsky for his advice and encouragement in this study and Mr. Robert Bowen for preparation of the photographic illustrations.

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# REVERSAL OF SYSTEMIC TOXIC EFFECTS OF SCOPOLAMINE WITH PHYSOSTIGMINE SALICYLATE

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With the widespread use of cycloplegic agents, mydriatics, and preanesthetic medications, anticholinergic intoxication occurs fairly frequently in ophthalmic patients. Physostigmine salicylate offers a readily available and rapidly effective treatment for the central anticholinergic syndrome. The following case reports illustrate our experience with this antidote.

## CASE REPORTS

A 75-year-old white woman in good general health was admitted for retinal detachment surgery. To dilate the pupils, one drop of 0.25% scopolamine and one drop of 10% phenylephrine was instilled in each eye every 10 minutes for two hours. Approximately 30 minutes following the final instillation of drops (calculated total dose: 3 mg scopolamine; 120 mg phenylephrine), the patient became somnolent and confused. The blood pressure was 150/80 mm Hg, the pulse rate was 66/minute with a regular rhythm, and they remained stable. Temperature was normal. She was oriented to time, place, and person although she was drowsy. Intermittently she picked at her clothes and brushed imaginary ashes into an ashtray. The skin was of normal color and the mucous membranes were dry. Deep tendon reflexes were normal and no pathologic reflexes were elicited. A diagnosis of toxic reaction to scopolamine was made. Despite the mildness of the reaction, physostigmine salicylate, 1 mg, was administered subcutaneously. Within five minutes the patient's sensorium had cleared significantly. Ten minutes after the injection of physostigmine, tearing and salivation were evident, and shortly thereafter, the patient urinated. She had no recollection of her behavior prior to the administration of physostigmine. The remainder of this patient's hospital course was uneventful.

A four-year-old black boy in previously good health was brought to the emergency room because of bizarre and unusual behavior originating several hours earlier. The child was irritable, combative, and disoriented. There was generalized muscular hypertonicity with sporadic, gross, nonrhythmic tremors of all extremities. Blood pressure was 120/65, pulse rate was 120/minute and regular, and rectal temperature was 99°F. The child's face was flushed, the skin was warm and dry, and the lips were fissured. Both pupils were dilated and nonreactive to light. Other Deep tendon reflexes were brisk, but equal. The remainder of the physical examination was normal.

On the basis of clinical findings, an atropine-like drug intoxication was suspected. The father, who wore an eye patch, claimed that the only medications in the household were eye drops (0.25% scopolamine, 10% Neosynephrine, and Cortisporin) prescribed for him following a recent eye injury.

Following subcutaneous injection of 5 mg of methacholine, there was no salivation, lacrimation, or perspiration noted. The injection was repeated 25 minutes later, again without effect. The failure to produce typical cholinergic signs strengthened the clinical impression of an atropine-like drug intoxication.[1]

The white blood count was 13,800 and the differential was normal. Blood glucose, serum calcium, electrolytes, and routine urinalysis were within normal limits and a ferric chloride urine test was negative.

Signs and symptoms persisted. Sixteen hours after admission, 0.25 mg of physostigmine sulfate was administered subcutaneously and repeated at 15-minute intervals. No change was noted following the initial dose; an increase in salivation appeared following the second dose; and tearing was noted during administration of the third dose. Ten minutes following the third and final dose, the boy responded to simple commands and was able to pick up small objects with either hand and walk without assistance. The pupils remained widely dilated and nonreactive but returned to normal within 24 hours.

An atropine-like drug was identified in the patient's blood and urine by ultraviolet spectrophotometry and thin layer chromatography. The remainder of the hospital course was uneventful, and prior to discharge, the boy admitted drinking "daddy's medicine" (the scopolamine eye drops).

## DISCUSSION

Intoxication from anticholinergic drugs should not be regarded as a benign reaction of short duration. Atropine and related drugs may produce dual central nervous system effects—stimulatory and depressant—with variations and overlapping between

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these extremes. Typical central nervous system manifestations include visual hallucinations, restlessness, ataxia, delirium, somnolence, stupor, and coma. Though usually of several hours' duration, these symptoms may persist for days.[2] Toxic reactions may result in the postponement of surgery or the compromise of surgical results. The agitated, delirious patient may seriously impair the functioning of the operating room, recovery room, hospital ward, or office.[3] At least six deaths from cycloplegic agents (notably atropine) have been reported.[2,4,5]

Although toxic effects appear to be dose-related in most cases, patients vary in their degree of susceptibility.[6] Those thought to be particularly susceptible include blond children,[7] patients with spastic diplegia, and those with Down's syndrome.[8] Carpenter[9] cites the case of an 82-year-old man with progressive mental deterioration who was given a total of four drops of 0.2% cyclopentolate (Cyclogyl) instilled topically. This patient developed acute mental decompensation which failed to revert with time. In otherwise healthy individuals, central nervous system symptoms arising from very small doses of anticholinergics may appear as an idiosyncratic response.[6,10] However, difficulty in administering drops, impurities contained in the solution, and variation in concentration due to evaporation make exact dosage of topical solutions difficult to ascertain.

The anticholinergic syndrome is identical to that seen in Jimson weed (loco weed) poisoning.[11] Beside atropine drops[2,5,12] and ointment,[2] usually of 1% concentration, other ophthalmic solutions incriminated include homatropine,[2] scopolamine,[10] and cyclopentolate.[13-16] In a double-blind study, Binkhorst, Weinstein, Bareta, and Clahane[14] presented evidence for a dose-related central nervous system toxicity from topical administration of cyclopentolate.

The use of the anticholinesterase, physostigmine, as an antidote to the central anticholinergic syndrome is well established.[3] The analogues, neostigmine (Prostigmin) and edrophonium (Tensilon), contain a quarternary ammonium group, and hence, they cross the blood-brain barrier poorly.[17] By contrast, the more lipid-soluble physostigmine, a tertiary amine, is readily absorbed and easily enters the central nervous system. Thus, it is an antagonist of both central and peripheral nervous system effects of anticholinergic drugs.[3] Parasympathomimetic drugs, as pilocarpine and arecholine, antagonize only the peripheral nervous system effects of anticholinergics and have no effect on the central nervous system excitation.[11,18]

In a series of 26 consecutive cases of anticholinergic intoxication treated with physostigmine salicylate, 1 mg intramuscularly or intravenously, Duvoisin[3] reported "gratifying results without exception." Crowell and Ketchum[19] administered physostigmine salicylate (5.0 mg/kg) to 33 healthy volunteers at various intervals after intramuscular injection of scopolamine (2.4 mg/kg). They concluded that while physostigmine failed to prevent onset of delirium, it could effectively and safely reverse the delirium once it occurred. The maximum reversing effect occurred 90 minutes after scopolamine injection.

The recommended adult dose of physostigmine is 1 mg, and it may be administered intramuscularly, intravenously, or subcutaneously at the time signs and symptoms of central nervous system toxicity are manifest. From our experience, a dosage of 1 mg/m$^2$ of body surface is safely administered in the pediatric age group. According to the studies of Weiss,[20] man is capable of totally eliminating this dosage within two hours. Accordingly, it may be necessary to repeat administration of physostigmine at this time should toxic symptoms recur. Should the initial dose of physostigmine be ineffective in reversing toxic symptoms, it can be repeated safely in 15-30 minutes.[20,21] In normal individuals without prior anticholinergics, a dose of 1 mg does not produce systemic reaction and Weiss[20] reported no ill effects after two doses given 30 minutes apart.

In view of the relatively innocous effect of physostigmine in the recommended dosage, we feel that all cases of anticholinergic intoxication should be treated.

## Summary

When a 75-year-old woman became somnolent and confused following instillation of 0.25% scopolamine and 10% phenylephrine eye drops, 1 mg of physostigmine salicylate administed subcutaneously resulted in complete clearing of her sensorium within five minutes. When a four-year-old boy ingested 0.25% scopolamine eye drops, he became irritable, combative, and disoriented with generalized muscular hypertonicity and gross, nonrhythmic tremors of all extremities. The pupils were dilated and nonreactive to light. After 16 hours, he failed to improve spontaneously; however, following three doses of 0.25 mg of physostigmine salicylate administered subcutaneously at 15-minute intervals there was rapid improvement.

Physostigmine salicylate is a rapidly effective antidote for the systemic toxic signs of the anticholinergic syndrome.

## Acknowledgment

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# ISOLATION OF STROMAL COLLAGENASE IN CORNEAL INFLAMMATION

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Although there have been numerous investigations of infections of the cornea, few report the nature of acute and especially chronic corneal inflammation. The present study establishes a model for acute and chronic corneal inflammation, and in addition, reports the isolation of a stromal collagenase.

## MATERIAL AND METHODS

Albino rabbits weighing from 2 to 4 kg were anesthetized with intravenous pentabarbital and topical tetracaine HCl. Corneal inflammation was produced by injection of 0.05 ml complete Freund's adjuvant in mineral oil (Difco) into the peripheral stroma (2-3 mm from the limbus) with a 25-gauge needle. The corneas were examined daily with loupe and light and were removed at various times before and after onset of inflammation.

The excised corneas were cut into quadrants and each inflamed area was bisected. One piece was saved for a collagenase assay and the other was placed in 3% glutaraldehyde in 0.2M sodium cacodylate buffer for 15 minutes. Following this, it was post-fixed in 2% osmium tetroxide in cacodylate buffer for one hour and dehydrated in alcohols and propylene oxide. Finally, it was embedded in Epon 812 and thick sections (5μ) were cut and stained with basic fuchsin and alkalinized methylene blue.[1]

The tissue saved for collagenase assay was dipped into mammalian Tyrode's solution. The epithelium was scraped free of the stroma and both were cultured on a rigid opalescent gel of 0.2% reconstituted collagen which was incubated at 37° C for up to four days.[2] Clearing of the gel surrounding the tissue explant indicated collagen lysis.

Additional pieces of corneas were excised seven days after intralamellar injection. The epithelium was scraped free and the stromas were trimmed to approximately 2 × 2 mm. Collagenase was harvested from these tissues by growing them in Dulbecco's medium.[3]

The effect of the harvested enzyme on the viscosity of a 0.1% collagen solution was tested using an Ostwald viscometer with a water flow rate of 53 seconds at 25° C and at pH 7.4. All measurements were made at 27° C. The effect of the harvested enzyme on the optical rotation of reconstituted collagen was determined using the MSP-3 photoelectric spectrophotometer at 25° C and 589 mμ.

Three methods were used to determine the cell origin of the stromal enzyme. The first was simply to repeatedly freeze-thaw stromas which were injected five days previously with Freund's adjuvant. This material was then transferred to gels of reconstituted collagen and incubated at 37° C for up to four days.

The second method was to apply puromycin $10^{-3}$M, which is an inhibitor of protein synthesis (and therefore enzyme synthesis), to the surface of the corneal explant twice a day for four days. For controls, alkali burns were produced in rabbit corneas,[2] and when ulcerations were noted, the epithelium which surrounded the ulcers was removed and soaked in puromycin $10^{-3}$M and assayed on collagen gels.

The third method was to reduce the circulating granulocytes by the intravenous injection of mechlorethamine HCl (nitrogen mustard), 5 mg three days before, and 3 mg on the day of intralamellar injection of Freund's adjuvant. Three, six, and 10 days later, the corneas were excised and bisected.

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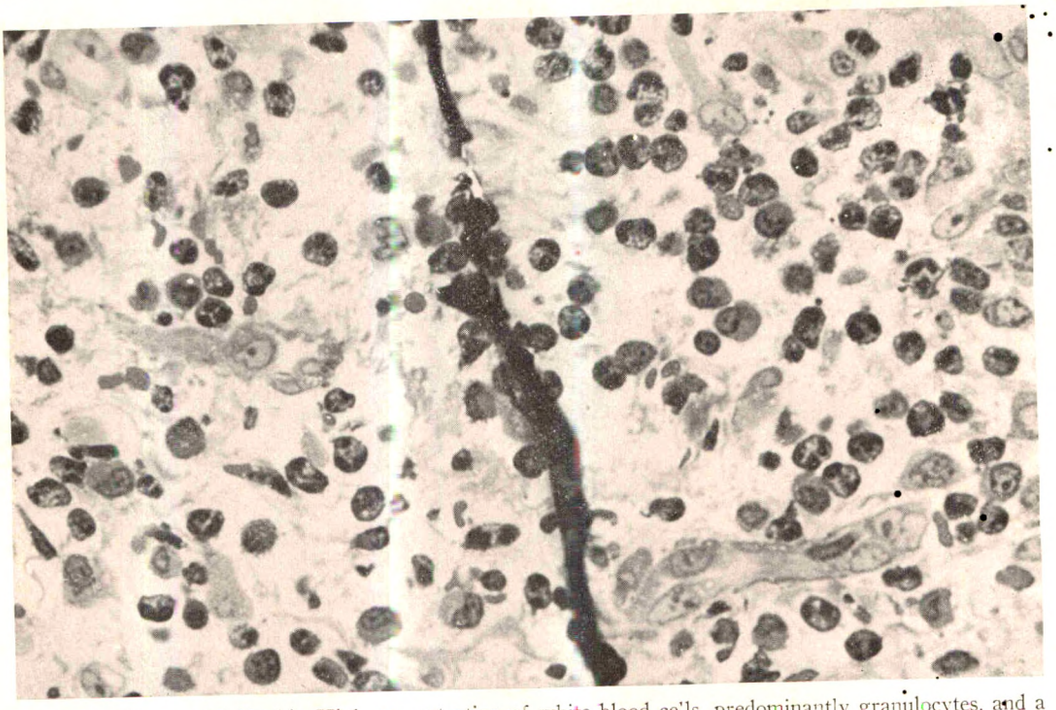


Fig. 1 (Brown and Hook). High concentration of white blood cells, predominantly granulocytes, and a few histiocytes or epitheliod cells (basic fuchsin and alkalinized methylene blue, ×400).

Half of each specimen was assayed for collagenase activity and the other half was examined histologically.

## Results

Grossly, the limbal blood vessels became dilated within 12 hours after injection of Freund's adjuvant. At 36 hours, the corneas were semitranslucent and slightly edematous. Neovascularization began at about four days postinjection. At this time, the stromas were grossly edematous and opaque. Histologic examination of the corneas at 24 hours showed granulocytes and an occasional mononuclear cell. The concentration of white blood cells increased markedly over the next 48 hours, especially in the area of the foreign protein. At four days, there were many granulocytes, and fewer monocytes and histiocytes (Fig. 1).

The cellular infiltrate increased in concentration until the third week, when the number and types of cells in the infiltrate became constant. Six weeks after injection of Freund's adjuvant, all cell types, but especially the granulocytes, began to decrease in number, and the stromal edema was grossly reduced. During postinjection weeks nine to 12 there were only a few histiocytes or epitheloid cells and granulocytes.

The epithelium from the inflamed stromas did not produce detectable collagen lysis in any specimen. On the other hand, in every instance culturing of the inflamed stromas produced collagen lysis at least 10 mm in diameter, beginning at 36 hours and continuing through nine weeks after intralamellar injection of Freund's adjuvant (Table 1).

The specific viscosity of the mixture of harvested stromal enzyme and reconstituted collagen at pH 7.4 gradually decreased over a one-hour period to about 60 percent of the original value (Fig. 2). The optical rotation measurement of reconstituted collagen (−442) was not changed by the addition of the harvested enzyme (−450).

All specimens that had been repeatedly freeze-thawed produced at least 10 mm in di-

TABLE 1

PUROMYCIN ($10^{-3}$M) AND COLLAGEN LYSIS*

| | Diameter of Lysis |
|---|---|
| Alkali-burned epithelium plus Tyrode's solution | >10 mm |
| plus puromycin | 0 |
| Granuloma (only stroma) puromycin | >10 mm |

* Five assays for each category.

ameter of collagen lysis. Puromycin completely inhibited collagen lysis by the epithelium from alkali-burned corneas (controls), but allowed lysis by the inflamed stromas.

The nitrogen mustard treatment schedule resulted in a circulating white blood count between 1200 to 1800 on the day of intralamellar injection. The granulocytes in the peripheral blood were mainly blast cells and were about 30% of the white blood cells. Specimens of the corneas of the nitrogen mustard-treated animals did not lyse the collagen gels at four, six, and 10 days after injection of Freund's adjuvant. The inflammatory reaction that resulted from injection of Freund's adjuvant was markedly reduced in comparison with those animals that had not received nitrogen mustard (i.e., there was less edema and neovascularization was delayed to the end of the second week). Histologically, there were many less white blood cells in the stromal infiltrate and these were heavily granulated.

## COMMENTS

Inflammation was consistently produced in the rabbit corneas by the intralamellar injection of Freund's adjuvant. This was first noted in 24 hours, reached its peak in intensity by the end of the third week and began to quiet after two months. The stromal cellular infiltrate surrounding the foreign protein was mainly granulocytic in the first few days, but later took on the characteristics of a granuloma with many large histiocytes or epitheliod cells in addition to the granulocytes. Tissue culture assays showed that the stromas of these corneas caused collagen lysis that was similar in quantity to that caused by the ulcerated alkali-burned cornea.[2] Harvest of the enzyme showed it to be a true collagenase because of its characteristic effect on the viscosity and optical rotations of reconstituted collagen.[4] The molecular weight of the enzyme and the dynamics of its inhibition will be reported.

Gross and Lapiere[5] demonstrated that animal collagenase is produced by living cells (epithelium and possibly fibroblasts) and that destruction of the cells by freezing stops collagenase production. An exception is the collagenase from the granulocytes which originates in the granules and can be detected only *after* cell disruption.[6] Another unusual feature of the granulocyte collagenase is that it is only weakly active against collagen fibrils. Since no other blood cell elements contain collagenase,[6] the only cells that could have produced the collagenase found in the inflamed corneal stromas were either the fibroblasts, the histiocytes, or the granulocytes. Collagenase was detected after freeze-thawing, which indicated that the enzyme originated from the granulocytes. A less likely possibility was that the enzyme was produced and stored in the tissues. Since stored collagenase has never been demon-

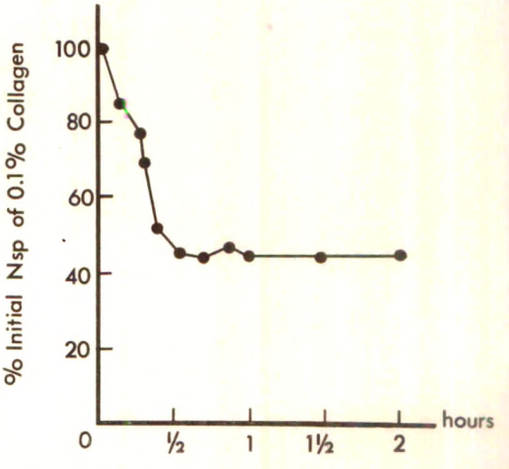



Fig. 2 (Brown and Hock). Graph showing a reduction in specific viscosity of reconstituted collagen after exposure to the stromal collagenase.

strated in tissues before, it is unlikely that the collagenolytic activity after freeze-thawing was from enzyme produced and stored in the tissues by the fibroblasts and the histiocytes before their destruction.

Soaking the inflamed stromas with puromycin, which is a potent inhibitor of protein metabolism, allowed collagenolytic activity. This indicates that the stromal enzyme was not a product of cell metabolism, which again points to the granulocytes as the collagenase carrier. Finally, when the number of the circulating granulocytes was reduced by approximately 80% by intravenous nitrogen mustard, collagenase production was not detected after intralamellar injection. Except for the findings that the harvested enzyme was active against heat-gelled collagen fibrils, the results of the present study indicate that at least part of the collagenase of the stromal granuloma originates from the granulocytes.

The obvious reduction in stromal edema and neovascularization in the animals pretreated with nitrogen mustard suggests that the granulocyte may also play a role in mediating various aspects of the inflammatory response. Studies are in progress to isolate this effect of the granulocyte.

Collagenolytic lysozomal enzymes have been isolated from inflamed tissues in other parts of the body. However, these were effective only when pH acidity fell between 3 and 5.5. There are no studies showing that the pH of inflamed tissue is in the acid range. Consequently, there is doubt that these acid hydrolases could destroy collagen in vivo. The present study demonstrates a neutral collagenase in inflammation of the corneal stroma, indicating the destructive potential of the inflammatory process. Though there was no gross loss of tissue in these inflamed corneas, preliminary study of the electron micrographs of the inflamed areas showed various types of collagen fibril alterations.[7]

Recently, we found that the collagenases of the alkali-burned cornea and the inflamed stroma are each inhibited by dilute concentrations of fresh serum. It may be that the minimal corneal destruction relative to the large amount of collagenase produced by the inflamed stroma is due to enzyme inhibition by elements in the serum. This inhibition would probably be related to new vessel ingrowth into the inflamed area. This will be expanded in a later report.

## Summary

Inflammation of the corneal stroma was produced in rabbits by the intralamellar injection of Freund's adjuvant. The inflammation progressed from a typically acute to a chronic granulomatous type of inflammation. A collagenase was isolated from the inflamed stromas and partially characterized. The enzyme appeared early in the course of the inflammation, thus indicating that it originated in the granulocytes.

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# NOTES, CASES, INSTRUMENTS

## NEW FIBER OPTICS COAGULATOR FOR MACULAR HOLES

C. M. J. VELZEBOER, M.D., G. TIESINGA, AND S. VAN RHIJN
*Amsterdam, Holland*

When scleral diathermy is performed in treatment of retinal detachment, localization and coagulation of posterior holes is difficult. This is especially true in treatment of macular holes, when a single coagulation is preferable, despite the fact that localization beforehand is not possible without a good view of the posterior scleral region. This may be extremely difficult or even impossible to attain, especially in strongly myopic patients.

In 1966, Oosterhuis[1] described a procedure in which fiber optics were used with the electrode attached. Thus the electrode formed the central part of an illuminated fundus area. The instrument was adequately curved but rather large for operation in the posterior area. Our technicians, Van Rhijn and Tiesinga, constructed an electrode using tiny silver wires to conduct the diathermy current together with a fiber optics light source. This electrode contains 47 silver wires and 220 glass fibers (Fig. 1). The wires are connected to a Siemens diathermy apparatus, the glass fibers with a simple fiber optic set (Fig. 2). A 4-V otoscope lamp, used on 3-V, was built into the handle of the instrument (Fig. 3). Silk is used for coating; impregnation is with polyester synthetic resin. Leakage and resistance must be measured. The mass of fibers is mounted in a stainless steel tube, and in the handle, a windowed aperture near the lamp provides an external indicator (Fig. 3).

We have achieved an electrode with a diameter of 2 mm and a coagulation surface of

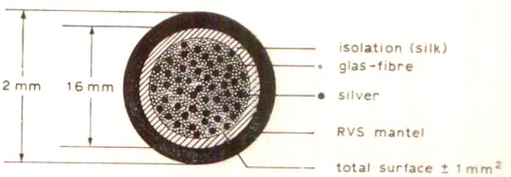



Fig. 1 (Velzeboer, Tiesinga, and van Rhijn). Cross-section of the electrode.

1 mm diameter. The illuminated area is also 1 mm in diameter, and identical with the coagulation.

The curvature is adapted to the shape of the globe. Thus the electrode can easily bypass a relatively small conjunctival incision without separating the muscle. In the posterior region of the eye it can be held in firm attachment to the eye (Fig. 4).

### OPERATING PROCEDURE

The electrode illuminated is passed to the posterior pole. Its position can easily be controlled by the surgeon, and when the correct position is reached, the surgeon can switch on the diathermy apparatus with the aid of a

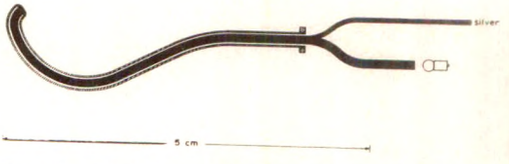



Fig. 2 (Velzeboer, Tiesinga, and van Rhijn). Interconnection of apparatus.

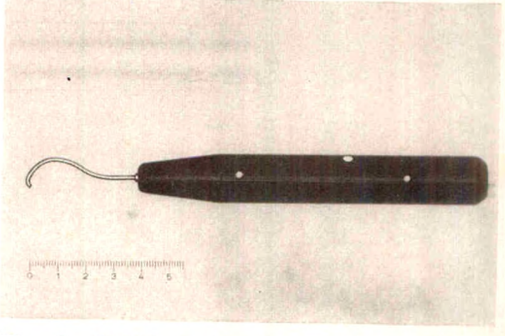


Fig. 3 (Velzeboer, Tiesinga, and van Rhijn). Handle of instrument.

From the Ophthalmological Department of the Free University, Amsterdam, Holland.
Reprint requests to Prof. Dr. C.M.J. Velzeboer, Ophthalmological Department of the Free University, De Boelelaan 1117, Amsterdam 1011, Holland.

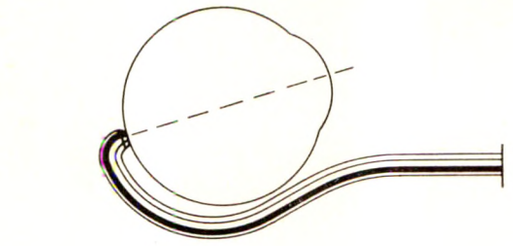



Fig. 4 (Velzeboer, Tiesinga, and van Rhijn). Because of its curvature, the instrument can be held in firm attachment to the eye in the posterior region.

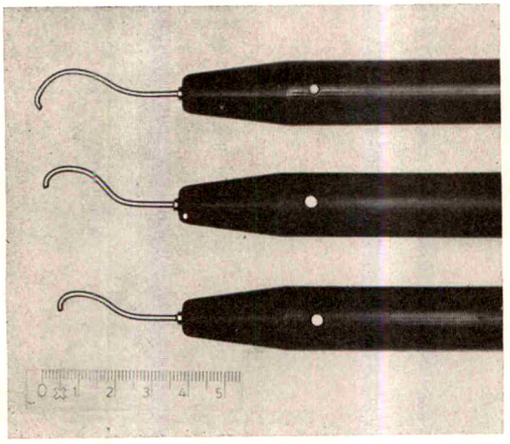


Fig. 5 (Velzeboer, Tiesinga, and van Rhijn). Series of electrodes designed for various procedures.

foot pedal and control the localization as well as the intensity of the coagulation. Using this apparatus, macular holes can thus be treated by a single, correctly placed coagulation.

A series of electrodes has been made in our department, each having different curvatures for macular holes and more peripherally located retinal tears (Fig. 5).

## Summary

A new fiber optics coagulator was designed for use in cases of macular holes. The electrode utilizes silver wires and glass fibers, and these are fused. The illuminated area is identical with the coagulation surface of the electrode, both being 1 mm.

## Reference

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# SIMPLE EPICANTHUS PROCEDURE

Sidney A. Fox, M.D.
*New York, New York*

A simple procedure for the repair of epicanthus is presented. There are no preliminary diagrams to mark out, no lines to measure, and no angles to calculate. Hence the surgery is tailored, as it were, to the epicanthus.

## Technique

The epicanthal fold is picked up and the base on each side is incised, the two incisions meeting below the fold to form angle-A (Fig. 1).

The resultant flap is dissected up, rotated medially, and flattened out. An incision is made along the upper border of the flap.

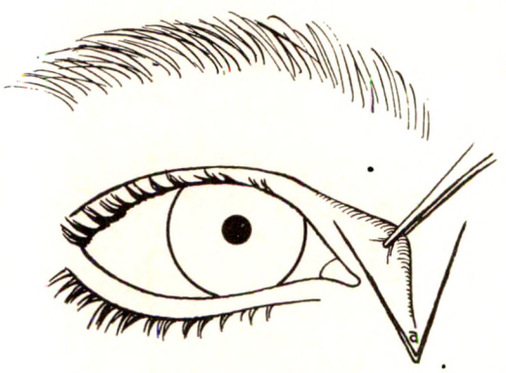


Fig. 1 (Fox). The epicanthal fold is raised and the base on each side incised, the lines meeting below at a point to form flap a.

From the Eye Service, New York University School of Medicine, and Bellevue Hospital.
Reprint requests to Sidney A. Fox, M.D., 11 East 90th Street, New York, New York 10028.

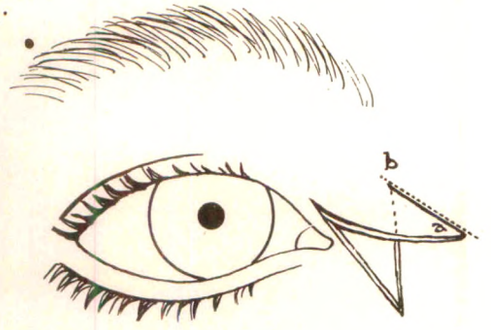



Fig. 2 (Fox). Flap a is dissected up and rotated medially. An incision is made along the upper border of flap and thus creating flap b.

This forms a second flap with angle-B at the apex (Fig. 2).

This second flap is mobilized and rotated down (Fig. 3); the two flaps are thus transposed. They are pulled firmly into position, the needles biting into the subjacent muscle tissue to prevent retraction, and sutured (Fig. 4).

## Discussion

Many of the procedures for epicanthus now in use require painstaking measurements and marking out of lines and angles before surgery. The Blair[1] and Mustardé[2] techniques are cases in point. The distinctive feature of this flap-transposition technique is that the size and shape of the flaps depend on the proportions of each individual epicanthus and not on preconceived diagrams, sometimes quite complicated, to which the epicanthus must be fitted in procrustean fashion. No preoperative planning or measurements are required. The surgery is simple, consisting only of three incisions, hence scarring is minimal and healing rapid.

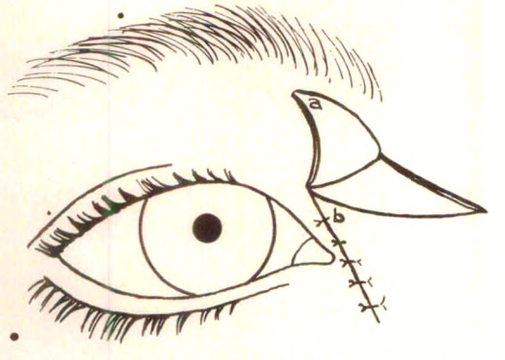



Fig. 3 (Fox). Flap b is dissected up, rotated downward and sutured medially.

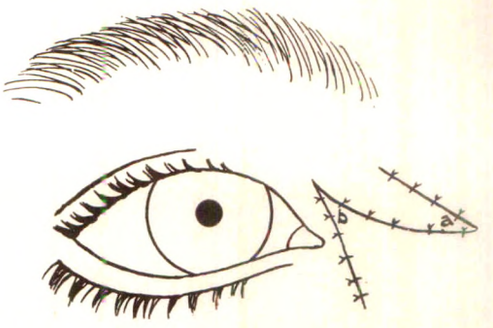



Fig. 4 (Fox). Flap a is then sutured into position.

In epicanthus inversus, the two preliminary incisions meet at an apex *above* the epicanthal fold with the rest of the surgery carried out as described.

## References

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2. Mustardé, J. C.: Epicanthal folds and problem of telecanthus. Tr. Ophth. Soc. U.K. 83:397, 1963.

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# FRENCH-EYE PIGTAIL PROBE FOR LACRIMAL CANALICULUS REPAIR

Matthew C. Kartch, M.D.
*Wayne, New Jersey*

Since 1969, several colleagues and I have been using a modified pigtail probe in the repair of the single laceration through a lacrimal canaliculus. The modification consists of tips containing a tiny "French" eye, with all edges rounded (Fig. 1). This modification avoids the problems of the "crochet hook" tips of the Worst[1] instrument, and the difficulties of threading the tiny eye in the Vincent instrument. The French eye also makes it possible both to push and pull doubled suture material. In a diagnostic situation, the

Reprint requests to Matthew C. Kartch, M.D., 330 Ratzer Road, Wayne, New Jersey 07470.

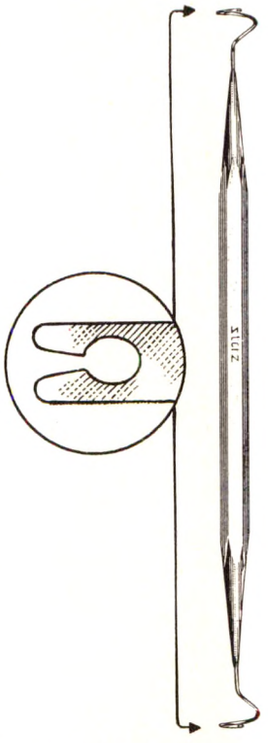


Fig. 1 (Kartch). The French-eye pigtail probe, with inset showing magnified detail of tips (illustration courtesy of Storz Instrument Co.)

instrument has been passed atraumatically in a 13-month-old child.


### Summary

A pigtail probe with French eye tips facilitates repair of torn lacrimal caniculus.


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## MODIFICATION OF THE DOUBLE OCCLUDER


Ferris F. Ketcham, M.D.

*Seattle, Washington*


A double occluder was modified so as to provide greater efficiency in eye examinations.



Fig. 1 (Ketcham). Photograph of the modified occluder.

The instrument measures nine inches in length which provides good balance. The occluder and Maddox rod each measure 2⅛ inches in diameter. All markings are printed on both sides of the instruments (Figure 1).

Adjacent to the Maddox rod is a white strip identifying the angle formed by the streak. The examiner may recognize readily whether the Maddox rod image is vertical or horizontal.

The pupillary diameters rulers read from left to right, regardless of the side used. A 1 mm pinhole is useful for evaluating visual acuity. The pinhole is located far enough from the occluder that it becomes quite obvious if the patient tries to use the pinhole to obtain better vision.

Accommodation lines, modified from the Lebensohn near vision charts, are provided on each side of the occluder. Manufacturing problems made it impractical to duplicate the original.


### Summary

This instrument measures nine inches in length with the occluder and Maddox rod 2⅛ inches in diameter. All markings are printed on each side of the instrument. Adjacent to the Maddox rod is a white strip indicating its angle. A pupillary diameter rule, a pinhole, and accommodation lines are provided.


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Reprint requests to Ferris F. Ketcham, M.D., 4615 35th Avenue Southwest, Seattle, Washington 98126.

# A TREPHINE FOR PRIMARY CORNEAL TRANSPLANT IN REPAIR OF CORNEAL LACERATION

ROBERT A. MOSES, M.D.
*St. Louis, Missouri*

AND

OLLE HOLM, M.D.
*Lund, Sweden*

Corneal lacerations crossing the optical zone are conventionally repaired by suture and allowed to scar. Later, transplantation of the scarred cornea may be performed. In many of these cases it would be desirable to perform the transplant as part of the initial repair procedure.

One way of supporting the lacerated cornea and of avoiding damage to the lens during trephination would be to insert some kind of protective plate through a limbal incision. This principal has been proposed for routine corneal transplant,[1-3] but it would seem highly undesirable to make a limbal incision in the presence of radial wounds.

Pittar[4] describes a corneal transplant punch in which the lower jaw resembles a button on a rod. The button is passed through a linear corneal incision into the anterior chamber and drawn upward through the bore of the upper cylindrical punch jaw. The present instrument* is an extension of Pittar's device.

The instrument consists of three parts, a lower clamp jaw, an upper clamp jaw, and a trephine:

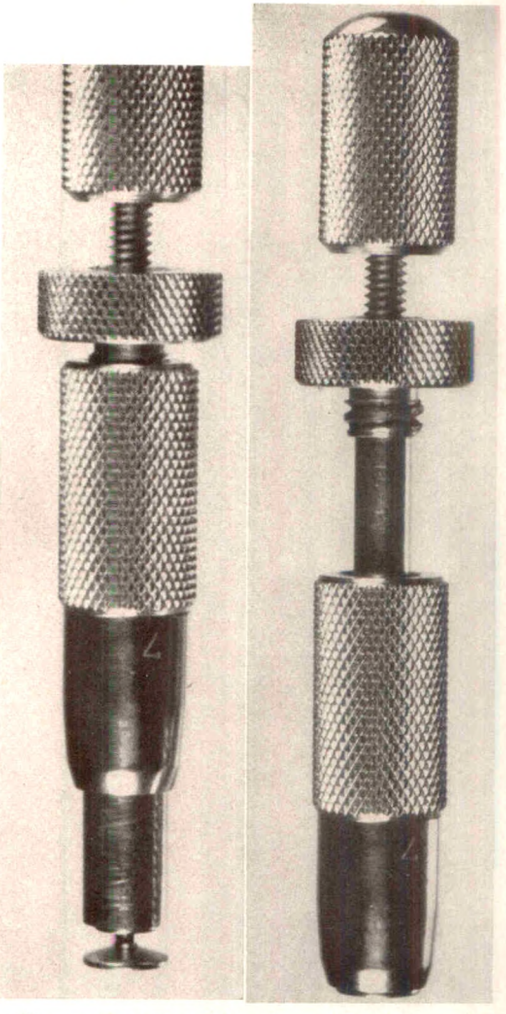


Fig. 1 (Moses and Holm). Left: Trephine for corneal transplant with clamp jaws open and trephine raised. Right: Trephine released.

The lower clamp jaw is mounted on a stem and can be inserted into the anterior chamber through the corneal laceration in a manner similar to passing a button through a buttonhole.

The upper clamp jaw is brought toward the lower jaw by turning the upper knurled knob clockwise, until the cornea is securely clamped between the jaws.

The trephine is held in a raised position by screw threads during the clamping procedure. It is freed by clockwise twisting until it slides freely along the shaft of the upper

From the Department of Ophthalmology, Washington University School of Medicine, St. Louis, Missouri (Dr. Moses), and the Department of Ophthalmology, University Eye Clinic, Lund, Sweden (Dr. Holm). This study was supported in part by Public Health Service Grant EY-00256 from the National Eye Institute.

Reprint requests to R. A. Moses, M.D., Department of Ophthalmology, Washington University School of Medicine, 660 South Euclid, St. Louis, Missouri 63110.

* The instrument was made to our specifications by the Storz Surgical Instrument Company, St. Louis, Missouri.

clamp jaw. A stop prevents the trephine edge from descending below the lower edge of the lower clamp jaw.

Figure 1 shows the instrument (left) with the clamp jaws open and the trephine blade raised, and (right) with the trephine released and down as far as it can go.

The trephine blade may easily be removed from the clamping assembly and attached to a simple handle for cutting the donor button.

## Summary

A trephine for primary transplant in corneal laceration incorporates a clamp to hold the corneal fragments in place and a stop to prevent the trephine blade from striking the lens.

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3. Sjögren, H.: Corneal transplantation with punch forceps. Acta Ophth. Scand. 36:394, 1958.

4. Pittar, C. A.: A technique of corneal grafting developed in New Zealand. Am. J. Ophth. 38:689, 1954.

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## Ophthalmic miniature

The Captain is walking his quarter deck,
With a troubled eye and a bended neck;
One eye is down through the hatchway cast,
The other turns up at the truck on the mast,
Yet none of the crew may venture to hint
"Our skipper hath gotten a sinister squint!"

Thomas Ingoldsby
*Ingoldsby Legends,* 1840

# MEETINGS, CONFERENCES, SYMPOSIA

EDITED BY THOMAS CHALKLEY, M.D.

## LENS SYMPOSIUM AT UTRECHT

More than 60 investigators actively involved in lens and cataract research met in Utrecht, The Netherlands, from August 23-26, 1971. The participants included anatomists, embryologists, protein chemists, ophthalmologists, and immunologists. The main subjects discussed were: (1) genetic transmission of RNA information for lens protein synthesis, (2) biochemical studies on protein structure and lens metabolism, and (3) embryologic differentiation and lens induction in vitro.

In the lens, the genetic code is transmitted from nuclear DNA to RNA during the process of cell to fiber differentiation following mitosis. Bell (Boston, U.S.A.) described a new type of lens DNA: cytoplasmic (also named metabolic or information DNA). This second type of DNA may provide another avenue for transmitting genetic information, or it may regulate protein or cell synthetic processes at a later stage in the life of the lens, and thus be responsible for cataracts developing throughout many years such as those of the senile type. Nuclear DNA and cytoplasmic DNA can be differentiated by inhibitors such as hydroxyurea, FDU and cytosine arabinoside.

The normal chemical structure of the lens proteins is of great significance for interpretation of possible molecular alterations resulting in cataracts. Electron micrographs of non-polysomal lens protein chains and filaments broken by 8 M urea, trypsin, and pronase were shown by Maisel (Detroit, U.S.A.). These chains of heteropolymers may correspond to the various subunits demonstrated chemically by Bloemendal and associates (Nijmegen, The Netherlands), Delcour and Papaconstantinou (Oak Ridge, U.S.A.), Li and Spector (New York, U.S.A.), and Bours (Utrecht, The Netherlands). The sequential analysis of large polypeptide chains of alpha-crystallin was accomplished by Croft (Oxford, England). This work is an important step in elucidating the secondary and tertiary structure of the lens proteins. The techniques are similar to those used for sequential analysis of insulin, hemoglobin, ribonuclease, etc. A sulfhydryl dependent binding of cortisol to lens proteins, mainly beta-crystallins was found by Ono and associates (Japan), and may point to additional pathogenetic mechanisms for steroid induced cataracts.

The areas of lens metabolism and transport of electrolytes were well covered. Changes in endogenous glycolytic and Krebs cycle intermediates were quantitated during lens exogenous energy deprivation by Cotlier (Chicago, U.S.A.) and Trayhern and van Heyningen (Oxford, England). Effects of increased intraocular pressure on lens metabolism were described by Hockwin (Munich, Germany). These alterations may result in the lens changes occasionally associated with acute increases of intraocular pressure. Reddy (Detroit, U.S.A.) determined protein-bound lens glutathione by a highly specific method. Discussion of these and other presentations was greatly enhanced by the participation of two pioneers in eye biochemistry: Zacharias Dische and Everett V. Kinsey.

Problems of embryonic lens induction were analyzed through genetic microphthalmia in mice by Campbell and associates (Edinburgh, Scotland) and congenital mouse aphakia by Zwaan (Boston, U.S.A.). A primitive lens develops from chick lens placodes cultured in vitro with the remaining optic vesicle even if separated by millipore filter or agar. The inducing factors diffuse through filters with pores of 20 nm or larger and the induction can be abolished by optic vesicle pretreatment with actinomycin D as shown by Jaaskelaneu (Helsinki, Finland)

and van der Starre (Utrecht, The Netherlands). The nature of the diffusable factor, probably a polypeptide, a glycosaminoglycan, or an enzyme, has not been determined yet.

Numerous papers on lens differentiation and regeneration were presented. Answers to the following questions were sought: (1) the regulatory mechanisms for lens mitosis in the epithelium, secondary migration and lens fiber formation; (2) genetic control and initiation of crystallin synthesis by lens fibers; (3) chemical factors in lens regeneration from iris of lentectomized salamanders. An outstanding 10-year review of his work, by Yamada (Oak Ridge, U.S.A.), indicates two phases occur in the regeneration of the newt lens: (1) dedifferentiation and (2) redifferentiation. Agarwal and associates (India) found more active rabbit lens regenerations after extracapsular extractions in eyes receiving fetal eyelid implants. These results are in contrast with other reports on rabbit lens regeneration. Cytological changes occurring after lens rotation in embyros were analyzed in detail by Génis-Galvez (Granada, Spain).

The social functions of the meeting were delightful, including a reception by Prof. Dr. F. van der Blij, Rector Magnificus of the State University of Utrecht. The pictures of Donders and Snelln on the walls of the University were brought to the attention of the Symposium participants, as a reminder of a long and distinguished tradition of eye research at this old Dutch university. Credit for the mammoth task of organizing the symposium should be given to Prof. of Anatomy and the Chairman of the meeting, Professor of Anatomy Dr. van Doorenmaalen, his committee and his able assistants, Dr. J. Bours and Mr. S. A. van Maarsen.

Edward Cotlier

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## SECOND CONFERENCE OF INTERNATIONAL SOCIETY OF GEOGRAPHICAL OPHTHALMOLOGY AND JERUSALEM SEMINAR

The Second Conference of the International Society of Geographical Ophthalmology and the Jerusalem Seminar on the Prevention of Blindness were held in Israel from August 23 to 27, 1971. Professors, clinicians, basic research scientists, nutritionists, physiologists and administrators from five continents representing 21 countries convened for the purpose of preventing blindness in both developed and developing countries of the world.

Among the internationally renowned essayists were Profs. Jules François and J. Charamis, President and Past-President of the International Council of Ophthalmology; Gunnar von Bahr, President, International Association for Prevention of Blindness; B. G. Bietti, President of the International League Against Trachoma; M. L. Tarizzo and Dr. Nizetic of the World Health Organization; Drs. H. A. P. C. Oomen, Fred Rodger, and Ida Mann, ophthalmic consultants to WHO; Profs. A. Nakajima and S. Mishima of Japan; Dr. Donald Lowe of Australia; Drs. V. Rambo, N. Chatterjee, G. Venkataswamy of India; Dr. N. E. Christy of Pakistan; Dr. G. G. Bisley of Kenya; Dr. Maurice Luntz of S. Africa; Dr. Elizabeth Cass of Canada; Dr. S. Delthil of France; Dr. V. Clemmeson of Denmark; Profs. A. Pirie and J. Dobree, and Drs. D. P. Choyce, J. Hudson, P. D. Trevor-Roper, and K. Wybar of Great Britain; W. Leydhecker of Germany; Drs. J. ten Doesschate and J. Schappert-Kimmijser of the Netherlands; Drs. A. Edward Maumenee, Gunter K. von Noorden, and Maurice Langham of Baltimore; Dr. Carl Kupfer, Head of the National Eye Institute, and many other leaders of ophthalmology.

The prevalence, geographic and ethnic distribution of eye diseases from Sweden, Japan, India, Israel, Denmark, Nigeria, Italy,

and the United Kingdom was the principal theme of one of the symposia.

Prevention of blindness in developing and developed countries was the principal subject at others. Under the first heading, keratomalacia, corneal opacification, onchocerciasis, and trachoma were discussed. Congenital and heredity eye diseases, diabetic retinopathy, herpes cornea, retinal detachment, glaucoma, cataract, and amblyopia were included.

Mr. John Wilson, C.B.E., Chairman of the Royal Commonwealth Society for the Blind, received a standing ovation for his inspiring report on the international scope of the prevention of blindness, spearheaded by the World Council for the Welfare of the Blind.

Social activities of the Congress included trips to the Walled City of Jerusalem, Bethlehem, the Dead Sea, a sound and light production "A Stone in David's Tower," a visit to kibbutz and other areas of historic interest. Receptions were held by the municipality of Jerusalem and the Israel Academy of Sciences and Humanities. A festive dinner was given at the Knesset building in Jerusalem honoring the Minister of Health.

Dr. and Mrs. I. C. Michaelson's kindness, hospitality, and friendship were paramount factors that contributed to the success of the seminar.

At the conclusion of the seminar the following report was drafted, approved and adopted:

1. CONTINUITY

(a) The Jerusalem seminar should be the first in a series of international conferences on the prevention of blindness. It is possible that the success of this conference was related to the fact that it was convened for a specific purpose and attracted scientists of various disciplines. It appears impractical for financial reasons to convene another international conference on this basis in the foreseeable future and it was accordingly agreed that an international prevention of blindness conference should be held in association with the International Congress of Ophthalmology in Paris in 1974.

(b) In the intervening years, regional conferences should be held in Africa, in Asia, and in Central and South America. The object should not be to discuss prevention in global, abstract terms, but to seek to formulate regional plans of action, indicating national and regional resources, the readiness of governments to take official initiatives, and the extent of overseas aid which might be available. To be effective, these regional conferences should be preceded by action at the national level.

(c) A study group on keratomalacia was formed during the Seminar. Other study groups should be formed, where required, as channels of communication in subjects in which there is a lively movement of professional interest and the possibility of effective action. Such groups might include onchocerciasis (the initiative being taken by F. C. Rodger); trachoma (B. G. Bietti); personnel (I. C. Michaelson). These groups would maintain contact by correspondence and would make their views known to WHO and the non-governmental agencies concerned.

2. INTERCONFERENCE ACTION

An interconference action committee should be formed. The World Prevention of Blindness committee which was formed some years ago as an executive link between the International Association for the Prevention of Blindness, the World Council for the Welfare of the Blind, and the World Health Organization, should be revived and strengthened for this purpose. It would have the additional function of initiating arrangements for future conferences and of assisting with the implementation of the proposals of the conference, particularly for the stimulation of national prevention of blindness committees. This committee, after the initial meeting which was held during the seminar, should continue its work by correspondence and through meetings, where practicable. The Royal Commonwealth Society for the

Blind should be invited to undertake the committee's administration. Expanding the former membership of the committee, it was agreed that the composition should be as follows: In addition to Chairman I. C. Michaelson, there will be four representatives of the International Association for the Prevention of Blindness and the International Congress of Ophthalmology. These are J. François, A. E. Maumenee, G. von Bahr, and John Holmes. There will also be three representatives of the World Council for the Welfare of the Blind, and these are John Wilson, Eric Boulter, and another yet to be nominated. This committee should remain in regular contact with WHO, UNICEF, and any other intergovernmental agency concerned. WHO should be requested to appoint an advisor and liaison, who would be invited to attend, as an observer, any meetings of the committee which might be convened and would receive all circulated correspondence.

### 3. National programs

It was recommended that the attention of national governments be called to the importance of the problem of blindness and loss of vision. Especially in the case of developing countries it may often be necessary to obtain a more complete and accurate information on the prevalence of ocular pathology in order to establish appropriate priorities. Whenever necessary and justified, requests for assistance could be addressed to WHO, either for carrying out this preliminary investigation or for setting up adequate facilities for coping with existing problems.

Depending on local circumstances, and with the aid of WHO and other agencies, teams could be organized which would attack the problem from a multiphase approach, beginning with the education of citizens in hygiene, dietary requirements, and when and where to seek medical assistance. An ophthalmologist should be recruited who would work in close collaboration with existing health services to develop a comprehensive approach to the local problems. He would practice clinical ophthalmology and the necessary facilities and equipment should be supplied to ensure that this care would be of high standard.

### 4. Publicity

There should be issued to the world's press, radio, and other publicity media, a brief statement on the effects of preventable blindness throughout the world and on the need for public awareness of the task and of the opportunity. This statement should be published at the conclusion of this seminar through Israeli media.

### 5. Publication

The main papers presented at this conference should be published, together with an introduction by I. C. Michaelson and A. E. Maumenee, summarizing proposals and ideas —e.g., the need for an interdisciplinary approach to the prevention of blindness, for the effective training and deployment of paramedical staff and public health ophthalmologists, the priority concern expressed over keratomalacia. The major emphasis was placed on prevention and research and it was the conclusion that this was not inconsistent with mass campaigns to treat and cure needless blindness in developing countries.

### 6. Register of ophthalmologists

The secretary general of the International Association for the Prevention of Blindness should establish a register of ophthalmologists and allied scientific personnel prepared to consider assignment in the developing countries. WHO and the nongovernmental organizations concerned should have access to this register.

William John Holmes
*Honolulu, Hawaii*

## BASCOM PALMER EYE INSTITUTE SEVENTH ANNUAL RESIDENTS' DAY

The Bascom Palmer Eye Institute held its seventh annual Residents' Day on June 4 and 5, 1971. The full-time faculty, residents, and fellows presented a total of 35 papers to a large gathering of alumni and local ophthalmologists.

Guy O'Grady and Frank Williams presented fundus photographic and fluorescein angiographic studies on the evolution of temporal retinal changes in premature infants with retrolental fibroplasia. Michael Rosenberg reviewed the fluorescein angiograms of two patients with secondary retinal detachments associated with the hypertension of toxemia of pregnancy. Follow-up angiography revealed changes in the pigment epithelium and choroid. Electrophysiologic studies of Stargardt's disease were reported by Russell Harner, and Robert Clark reported on the histories and follow-up examinations of 10 patients with posterior multifocal placoid pigment epitheliopathy. He reaffirmed the good visual prognosis in this disease despite marked pigment derangement. Central retinal vein occlusions were reviewed by William East, who attempted to relate anticoagulant therapy and good visual prognosis.

Ken Wallace reviewed eight patients with melanocytoma of the optic nerve, five of whom were followed for several years. He confirmed the benign nature of this tumor in respect to visual acuity and visual fields. Henry Clayman reported two interesting cases of retinal pigment epithelial derangement following papilledema in children with acute leukemia who had central nervous system involvement. The histologic findings were correlated with the clinical photographs. Both children had received multiple systemic and intrathecal antimetabolites prior to their deaths. Charles Wilkinson noted a 12% incidence of preretinal membrane formation in the macula after successful scleral buckles on 297 detached retinas. Possible contributing factors were discussed. Donald Gass presented four cases of bullous non-rhegmatogenous retinal detachment which appeared to be caused by idiopathic central serous choroidopathy. Fluorescein angiographic studies were reviewed and the good visual prognosis without treatment was emphasized. Carmine Bedotto discussed the design, surgical application, and radiation safeguards referable to the cobalt-60 applicators which are of growing interest in the therapy of ocular tumors.

Another group of papers dealt with basic research of the retina and vitreous. Helmut Buettner utilized autoradiographic techniques to study protein synthesis and turnover in normal, detached, and reattached owl monkey retinas. It appeared that the increased protein synthesis after reattachment correlated with the structural regeneration in the various retinal layers. The effect of collagenase and chymotrypsin on vitreous viscosity was studied by Randolph Martin. He found that concentrations high enough to affect vitreous viscosity in the owl monkey were also retinotoxic. Steven Charles recorded the early receptor potential in detached and reattached owl monkey retinas and found a slow disappearance after detachment and a gradual return to normal following reattachment. A model for the extracellular recording of the ERG, dark adaptation, and flicker fusion on transplanted photoreceptors of the fly (Muscea volitantes) was reported by Daniel Eichenbaum. He was able to record normal data from his transplanted photoreceptors. Finally, Jay Pollack and Duco Hamasaki recorded a reduced ERG and late receptor potential in light-deprived kittens. The recordings returned to normal after the kittens were exposed to ambient light conditions for eight weeks.

Charles Israel reviewed a series of biopsy specimens and compared the histologic diagnosis with the referring clinical impression. This study re-emphasized the need to biopsy eyelid lesions for accurate diagnosis. Wilson

Wallace presented a historical review of hydrophilic contact lenses and their current status in the United States. Beth Friedland, a Coral Gables high school student, isolated a non-lysozyme, low-molecular-weight, tear factor with 200 times the antibacterial activity of the lysozyme factor. J. Lawton Smith surveyed cases of interstitial keratitis, with emphasis on the serum FTA-ABS test. Three papers were devoted to infectious ocular problems. Richard Forster presented a follow-up on pimaricin-treated fungal corneal ulcers. Since 1968, when pimaricin was first used clinically, 19 of 21 Fusarium solani corneal ulcers have been successfully treated, with 15 patients achieving a visual acuity of 20/60 or better. Experimental bacterial endophthalmitis was easily produced in rabbits by David Tucker. The organism could be isolated by anterior chamber paracentesis after the onset of clinical endophthalmitis, and therefore this diagnostic procedure was recommended. Finally, Bobby Shewmake reviewed cases of orbital cellulitis and revealed the importance of para orbital sinus infection in these cases.

Gary Wallace reviewed 144 cases of surgically treated exotropia and correlated the type of surgery with the results. John Flynn discussed his findings on retinal rivalry in normal, anisometropic, amblyopic, and strabismic amblyopic patients. A method for utilizing random dot stereograms to study binocular vision, neural models, and retinal rivalry was proposed by Michael Hyson and T. Shipley.

The production of acute intracranial hypertension was followed by a rise in intraocular pressure after a short latent period, and Antonio Montalbo postulated several mechanisms for this occurrence. Joel Glaser discussed a 23-year-old woman with a depressed linear scalp lesion (en coup de sabre), optic neuritis, and ocular muscle palsies. These two findings have never been reported in association with facial hemiatrophy. Eight interesting cases of periodic alternating nystagmus with its differential diagnosis were presented by Dale Davis. And finally, Ronald Seeley reported three patients with hypoplasia of the optic nerve, two of whom had cecocentral scotomas and the third had a temporal hemianopia.

The fields of glaucoma and the lens were represented by three papers. Douglas Anderson and Ralph Kirsch presented material on the normal and glaucomatous optic cup. They feel that glaucomatous cupping may be recognized by recession of the entire anterior disk surface, especially superiorly and inferiorly, resulting in a vertically oval cup. Recent interest in trabecular surgery for congenital and medically uncontrollable open-angle glaucoma has resulted in the use of trabeculotomy for treating a small number of patients over the past year. Thomas Coulter reviewed some admittedly early but optimistic results. Joel Kramer and O. E. James continued the annual review of the intraocular lens implants which was begun in Miami several years ago.

Dr. Norton closed the meeting with a presentation of the characteristic retinal detachment that results when there is vitreous traction extending from a cataract wound to the vitreous base. A vitrectomy through the pars plana converts this situation from a problem detachment into one that is more conventionally aphakic.

Following the presentations on Friday, June 4, the alumni association held a business meeting at which new officers were elected, followed by the annual Residents' Day dinner at the Miami Springs Villas. The evening was concluded with remarks on the future of the Bascom Palmer Eye Institute and ophthalmology in Miami by Edward W. D. Norton

Carmine Bedotto

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## THE SEMICENTENARY OF INSULIN

Frederick Grant Banting (1891-1941), a qualified orthopedic surgeon who received the Military Cross in World War I, returned to Canada to find private practice disappointing. He then secured an appointment in the Department of Physiology of the University of Toronto. While seeking a research project, he read an article by Moses Barron in November, 1920, which noted that after ligation of the pancreatic duct in dogs, the zymogenous acinar cells degenerated but not the islets of Langerhans. Actually, A. J. Carlson had demonstrated this in 1914, but, like Barron, he had not tried injecting an extract of the degenerated pancreas in dogs rendered diabetic by complete pancreatectomy. This Banting resolved to do. Though Professor Macleod knew that Zuelzer (1908) and others had found injections of pancreatic extracts to be very toxic, he granted Banting's request for 10 dogs and the use of the laboratory for two months. Charles H. Best, aged 22, who was interested in carbohydrate metabolism, was assigned to assist him. They began working on May 16, 1921, and under aseptic precautions they prepared a crude extract of the degen-

erated pancreas from their first dog. A small portion of the extract was injected intravenously in a depancreatized dog. The blood sugar fell from 200 to 100 mg/100 ml in two hours. They repeated these experiments until they achieved 10 successes. On Macleod's return from Scotland, he insisted on the continuation of their investigation until they accumulated 60 additional positive results.

On January 11, 1922, the first human patient was treated cautiously at the Toronto General Hospital. Best had found that an effective extract could be prepared from beef pancreas by alcohol extraction which dissolved the insulin and inhibited the digestive ferments. Macleod asked J. D. Collip of the University of Alberta to aid in its purification. Partial success was accomplished by fractional precipitation of the alcoholic extract. Further purification was later effected by isoelectric precipitation. In 1923, the Nobel prize was awarded to Banting and Macleod which was shared by them with Best and Collip.

The word "diabetes," meaning "to run through a siphon," originated with Aretaeus of Cappadocia (c. 81–138); the modifier "mellitus" was added by Cullen (1708–1890). In 1880, Heyl first noted diabetic lipemia retinalis. This appears when the fat content of the blood reaches 5%. Before insulin was available, its appearance signalled oncoming coma and a fatal outcome. Now, after a single injection of insulin, the retinal picture changes to normal in a few hours. In 1909, MacCallum enunciated the relationship of the islets of Langerhans to diabetes. In 1916, David Riesman described the soft eyeball in diabetic coma. In 1930, Houssay observed an improvement of diabetic symptoms in depancreatized animals after hypohysectomy.

Macleod recalled that a fellow Scotsman, Sharpey-Schaefer, used the word insulin in 1910 for the internal secretion of the pancreas, and he adopted the term. Insulin hydrochloride was followed by crystalline zinc insulin (1926), both rapid acting, with peak activity in two to four hours. Then came the long-acting protamine zinc insulin (1936), with its greatest effect at 12-24 hours, globin insulin (1942), NPH insulin (1946), and lente insulin (1950), all with intermediate activity. The usual regimen is a mixture of NPH and regular insulin in the indicated dosage before breakfast, and a small amount of NPH after supper. Analysis revealed that insulin is a protein with 11 amino acids and an essential S-S bond.

Experimental permanent diabetes can be effected surgically by complete pancreatectomy (Minkowski and von Mering, 1889), or by intravenous injection of alloxan, a derivative of uric acid (1943). After injection of 200 mg/kg in the ear vein of a rabbit, the beta cells of the islets of Langerhans disappear in six hours, but the alpha cells are not affected. After the injection, a transient hypoglycemia occurs, due to the liberation of insulin, followed by a permanent hyperglycemia. Cataracts are evident in four to six weeks, the opacities starting in the posterior subcapsular cortex, as in diabetes in man.

The vascular disorders incident to prolonged diabetes in man are now our greatest unresolved problem in the management of diabetes. Early and persistent diabetic control can only postpone the advent of retinopathy. Nettleship (1888) described proliferative diabetic retinopathy with neovascularization and noted that vision was usually lost within a few years. The prognosis has not changed. The vascular alterations, like the susceptibility to infection, are not a consequence of hyperglycemia but depend on biochemical changes not yet discovered.

In establishing the diagnosis of diabetes, a blood sample taken two hours after a regular meal may be more helpful than the fasting blood sugar. The former should not exceed 160 mg; the latter, 120 mg. In a glucose tolerance test, the patient takes 100 g glucose in water flavored with lemon juice, and the blood sample taken two hours later should be under 120 mg.

Thanks to insulin, eye operations on a dia-

betic patient are uneventful if the diabetes is so controlled that the patient is able to take a diet that is nutritionally adequate without developing hyperglycemia or glucosuria. The usual carbohydrate allowance must not be restricted. Preoperative resolution of any infection is imperative. On the day before surgery, liquids should be supplied freely, and food that is easily assimilated should be given within three hours of the operation. Since acidosis is more serious than glycosuria, liquid carbohydrates, such as diluted milk, orange juice, and gingerale, should be given three hours after surgery and allowed freely during the next 24 hours. At least 100 g of carbohydrate should be provided daily, giving enough insulin to insure utilization. After a long operation, such as that for retinal detachment, dextrose should be administered intravenously.

James E. Lebensohn

## A MEMENTO

On September 22, 1896, there appeared at the University Eye Clinic in Leipzig, Germany, an 18-year-old electrician by the name of Georg Sturm who had sustained a perforating injury to his previously normal right eye. He had been seen there previously, in 1891, for a left esotropia. An operation had been recommended, but the patient did not report for it. When seen in 1896, the left eye was found to be severely amblyopic, the vision being reduced to counting fingers at 6 m. The right eye had to be enucleated and the patient was discharged four days later. When he returned after three days, he stated that he saw double with his remaining eye and three weeks later the difficulty continued. On January 4, 1897, the vision had improved to between 6/60 and 6/36 at distance, and J-8 at 10 to 12 cm at near. Because of the confusion which it caused, the diplopia had become more annoying, especially in reading. The young assistant who saw the patient was puzzled and fascinated by the case and described him not only to his chief, Prof. Sattler, but also to the master of visual physiology, Prof. Hering, whose Physiologic Institute was next door to the Eye Clinic, and who performed a number of experiments with the patient.

The young assistant was Alfred Bielschowsky. The study of this case of monocular diplopia launched him on his life-long career in the field of neuromuscular anomalies of the eyes. With his extensive and sound physiologic background, acquired through Hering and through collaboration with F. B. Hofmann, then an assistant of Hering's, and his intensive and continued clinical work, Bielschowsky became the outstanding expert in strabismus in continental Europe during the first third of our century. With his move to the United States in 1935, he extended his salutary strabismus studies among the American ophthalmologists who had always had a special interest in the field.

Bielschowsky was born 100 years ago this month on December 11, 1871. It is meet and just that ophthalmologists here and the world over should be reminded of this centenary.

Hermann B. Burian

## CORRESPONDENCE

### APHAKIC DETACHMENT

Editor,

American Journal of Ophthalmology:

Current remarks in papers and advertisements give the impression that chymotrypsin in cataract extraction is used only at the surgeon's discretion and then in patients under 60 years of age.

From the cataract surgeon's point of view, estimates of detachment in intracapsular cases vary only a little. In 1964, Barraquer[1] recorded 3.7% without chymotrypsin, and 2.9% with chymotrypsin, while in 1967, Pasino[2] recorded 2.6% with chymotrypsin. Such small percentages can reasonably be considered inevitable, but seen from a retinal detachment surgeon's point of view, a

very different picture emerges. In 1964, Norton[3] found that 30% of his detachments were aphakic. The realization that such a small cataract percentage can mean such a large detachment percentage shows that any small improvement in the cataract series can result in a large reduction in the total number of aphakic detachments.

So it may be of interest that in a recent series of 1200 intracapsular extractions, Kelly[4] (1969), with the intention of preventing aphakic detachment, reduced the rate to 0.2% by the use of a combination of well-known procedures (including zonulysis in all cases).

Therefore it is worth considering once again what factors can be modified in intracapsular extraction so as to reduce the small incidence in the cataract series. It is accepted that for highly myopic cases, or for those that have previously had an unexplained aphakic detachment, extracapsular extraction is performed; these circumstances formed some of the reasons for developing the ultrasonic method of Kelman[5] 1967.

Sachsenweger[6] presented two series in 1966, one with zonulysis and one without, in which there was no difference in the incidence. In his opinion the main causes of aphakic detachment were loss of vitreous with its sequelae and a leaking wound, and to a lesser degree a predisposition to detachment in myopic degeneration and in old trauma. By using a beveled section and seven corneal sutures in the superficial part of the section, and suitable anesthesia, we can remove these main causes. Then if a detachment does not occur immediately, any predisposition can be eliminated to some extent by light coagulation, laser and cryotherapy, as soon as the predisposed areas can be seen postoperatively.

Schepens,[7] however, had already warned (1951) that small dialyses and breaks closely related to the meridonal folds over the teeth of the ora of the normal retina can also be responsible for detachment. This trauma might be caused by a section that distorts the eye in the same area where the tears arise. A blunt Graefe knife could act in this way. Therefore, not only should the distortion be avoided, but the lens should be extracted in such a way that there is no excessive pull on the zonule, so that no holes are torn in the teeth by direct or indirect pull. Since the zonule can be strong, even at 85 to 90 years of age, its strength should presumably be reduced in all cases.

For the extraction with the help of zonulysis the erisophake is possibly the most gentle method, but any method carries risk.

Quite the most dangerous method a cryoextraction when used without zonulysis, because of the immense strength of the cryoattachment to the lens, which is said to be 200 time as strong as that of the capsule forceps. This can lead to an easy extraction in which the resistance of the zonule is not fully appreciated. This appreciation is further diminished because one has to consider other problems at the same time, such as avoidance of attachment to the iris. Damage to the teeth of the ora, due to the omission of zonulysis, may begin to show an effect over a wide geographical area in producing a higher percentage of aphakic detachments, but this increase would not be appreciated until either a detachment or cataract surgeon published a series.

May I therefore make a plea for the use of zonulysis in all uncomplicated cases of intracapsular extraction.

T. Stuart-Black Kelly
*Bath, England*

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## BOOK REVIEWS

THE VISUAL FIELDS. A TEXTBOOK AND ATLAS OF CLINICAL PERIMETRY, 3rd ed. By David O. Harrington. St. Louis, C. V. Mosby, 1971. Clothbound, 394 pages, table of contents, bibliography, index, 341 black and white figures, and nine color figures. $21.50

This textbook should be on hand in every opthalmic office, for it is a complete exposition of the techniques of plotting the visual fields on the various instruments designed for this purpose and of their interpretation. Part I includes six chapters which detail the anatomy and vascular supply of the visual pathways, the characteristics of the normal visual field, and the methods of testing the visual fields. Part II is comprised of 10 chapters. This part is devoted to a beautifully illustrated description of the abnormalities encountered in disease processes in each portion of the visual system.

The book is written in a clear, well-organized fashion which should fulfill the needs of every ophthalmologist and his visual field technician.

In general, this third edition is similar to thet second, except that the headings of the various sections are more clearly printed, the illustrations are more closely associated with the text, and in each chapter some pertinent paragraphs have been added. There have been relatively few deletions. Also, chapters 10 and 11 on retinal lesions and glaucoma, respectively, have been rewritten and revised. The index of this edition has been vastly improved. Forty-two recent references have been added to the extensive bibliography.

The author does not mention the theory of macular sparing in occipital lobe lesions which ascribes this phenomenon to overlapping vascular supplies from the calcarine branch of the posterior cerebral artery and the posterior cortical branches of the middle cerebral artery, a theory which seems to the reviewer the most attractive of any so far advanced. In the reviewer's opinion, to accurately depict the visual defects and to most efficaciously localize the site of the responsible lesion, the following isopters should be shown: (1) that of the smallest target visible to the patient, (2) that of the largest target that shows a defect, and (3) that of the smallest target, if any, that produces a normal visual field. Many of the drawings would benefit from additional isopters, although presumably some were deliberately omitted to emphasize the pertinent findings. Finally, figure 15-4, although said to demonstrate right homonymous upper quadrant anopsia due to a ruptured aneurysm of the anterior communicating artery, is depicted only with tiny targets on the tangent screen and with flicker fusion frequency fields in the same area. The peripheral isopters of these fields are necessary for localizing the affected portion of the visual pathway; the defects as shown could well be ascribed to visual cortex involvement in the left occipital lobe.

However, these are minor matters which detract very little from the excellence of this book.

Robert W. Hollenhorst

STRABISMUS - DIAGNOSTIK - SCHIELFORMEN THERAPIE. By J. Lang. Bern, Switzerland, Verlag Hans Huber, 1971. Paperback, 206 pages, table of contents, references, index, 58 black and white figures. Fr. 28

This small volume summarizes well the author's views on certain aspects of the neuromuscular anomalies of the eyes—that is, his views on small-angle strabismus (what he has called microtropia), congenital stra-

bismus, and strabismus of late onset (termed by Lang, normosensory strabismus).

It contains nothing new for the expert in the field, who may well challenge some of the author's statements, presented frequently as his beliefs, without supporting evidence. It is questionable to what extent the book is useful to the novice or the practicing ophthalmologist, to whom it is primarily addressed. The overview of the neuromuscular anomalies is very cursory. This also applies especially to the discussion of the normal sensory and motor cooperation of the eyes. In part, this is due to the extremely concise way in which the book is written. Thus, the statement (p. 24) that the horopter is "a purely imaginary plane in space in the center of which is the fixated object" is followed immediately by the sentence: "Only objects lying on the horopter surface stimulate corresponding retinal points." The idea that object points stimulating retinal elements can be on a purely imaginary surface must surely be confusing to someone who meets these concepts for the first time and tries to understand them. From a didactic point of view, the book has certain other shortcomings. For example, the Maddox Wing test and the Livingston gauge are recommended, but nowhere in the book are these tests described.

One of the attractive features of the book is the author's general attitude toward therapy. He warns against the uncritical application of a given type of treatment to all forms of strabismus without distinction, and against being overly impressed by unwarranted success claims for new or newly resurrected therapeutic measures.

The index is inadequate, but the book is pleasing typographically and its format and flexible binding handle well.

Hermann M. Burian

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MANUAL OF CLINICAL MYCOLOGY, 3rd ed. By Norman F. Conant, David Tillerson Smith, Roger Denio Baker, and Jasper Lamar Callaway. Philadelphia, W. B. Saunders, 1971. Clothbound, 755 pages; table of contents, index, 299 black and white figures. $13.50

This is the third edition of one of the three standard textbooks of clinical mycology written in English. Unfortunately, none of the available textbooks cover mycotic eye disease with any attempt at completeness. This latest edition is no exception. There are only seven pages devoted to mycotic keratitis and little emphasis has been placed on the opportunistic infections. These "diseases of medical progress" are associated with the use of steroids, immunosuppresives, and radiation therapy. Further, the authors might have added several more species to their list of agents which cause ocular infection, such as Allescheria and Cryptococcus. A discussion of the current thinking concerning the role of fungi in chorioretinitis would surely have been of interest.

This latest edition has been updated to include the newer therapeutic agents. Amphotericin B and nystatin are discussed as eye medications, but no mention is made of their extreme toxicity to the cornea. A discussion of the new agent, pimaricin, is lacking in this volume.

In spite of the text's shortcomings concerning ocular mycology, it remains one of the leading sources of information on the classical diseases of medical mycology. The writing is generally good and the material factual. The references are adequate and chapter 31 on contaminants contains absolutely essential information for every mycologist. This chapter is coupled with a fine methods appendix which make this manual indispensable to the laboratory worker. This latest edition of a classical textbook on medical mycology can be of great value to the practicing generalist.

J. Terry Ernest

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A Synopsis of Ophthalmology, 4th ed. By J. L. C. Martin-Doyle. Baltimore, William and Wilkins, 1971. Clothbound, 280 pages, table of contents, index, five black and white figures. $9.75

This is one of a series of synopses of medical specialties written and printed in Great Britain and distributed in the United States. The synopsis is aimed at the senior medical student, the busy general practitioner and the ophthalmologist in training, as an examination preparation manual. The author's primary sources are textbooks of ophthalmology written by Sorsby and Duke-Elder, and Wolf's *Pathology of the Eye*.

One may, with the above information, readily predict the outcome: a virtual dictionary of ophthalmology which is remarkably inclusive and extremely well organized Some of the material is outdated, and controversial points of management are often not presented. References are sparse at best, but the index is quite thorough and useful. The book would fulfill the author's purposes quite adequately except for the extraordinary paucity of illustrations. I would therefore recommend to medical students or busy practitioners one of the standard ophthalmology textbooks which are more appropriately illustrated and available at a cost within a few dollars of this text.

Paul E. Romano

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Spirochetes in Body Fluids and Tissues. Edited by James N. Miller. Springfield, Illinois, Charles C Thomas, 1971. Paperback, 72 pages, table of contents, index, 17 black and white figures. $5.50

This little monograph is an outgrowth of a seminar held at the Venereal Disease Research Laboratory in Atlanta, Georgia, in 1969. A committee was appointed, drawn from workers in the field of experimental syphilis and other treponematoses, to suggest standardized methods and reagents. The committee consists of Dr. Miller, the editor, and Virginia H. Falcone, Bruce Golden, Charles W. Israel, U. S. G. Kuhn III, and Robert M. Smibert. The book gives recommended procedures for animal inoculations, serologic tests on blood, spinal fluid, and aqueous humor, and technical details are given concerning paracentesis, lumbar puncture, and staining methods for treponemes in tissues. An appendix lists additional references, commercial companies, and reference laboratories. The manual is concise and well done. It will be of little immediate help to the practicing ophthalmologist for it is really not aimed at him. It will be of very great help to the laboratory investigator in experimental treponematoses.

J. Lawton Smith

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Traitement Chirurgical des Affections Oculaires. By L. Guillaumat, L. Paufique, and R. De Saint-Martin. Paris, Editions Doin, 1971. Clothbound, 580 pages, alphabetical index, table of contents, 115 B/W figures. 188.00 F

This first of two compact volumes presents a comprehensive review of ophthalmic surgery. In contrast to most American texts dealing with surgery, there are relatively few illustrations. This has allowed the authors, who are the Deans of French Ophthalmology, to devote more space to discussion of operative indications, procedures and complications.

An important section is devoted to anesthesia for ocular surgery followed by a consideration of preoperative care to enhance surgery and emergency operative procedures.

In systematic fashion the authors deal with the surgery of various types of cataracts, glaucomas, traumas, foreign bodies, and chemical and radiation burns to the anterior segments.

It is interesting to note that the authors

list as a routine technique the closure of a cataract incision by a continuous, locked, virgin silk suture. Apparently this technique is well accepted in Europe while it has only been recently described in the Western hemisphere. Also reported as standard procedures are various operations involving the canal of Schlemm and the trabeculum in the treatment of refractory glaucoma.

This volume is of especial merit because of its discursive and authoritative approach to common surgical problems.

Marcel Frenkel

MARKETS FOR THE MEDICAL AUTHOR. John G. Deaton. St. Louis, Warren H. Green, Inc., 1971. Clothbound, 92 pages, table of contents, index. $10.00

A listing of some 336 medical and scientific journals is divided into 25 specialties. Eight journals are listed in ophthalmology; in addition there are listings of university presses, medical book publishers, and paramedical journals, house organs, and medical newspapers. The little volume provides a useful source of addresses.

Frank W. Newell

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OPHTHALMIC MINIATURE

Of the poets who used copious colour images, Shelley and Keats were to the fore, Shelley generally using straightforward and commonplace colour names (as yellow, blue, purple, green, etc.), whereas Keats preferred to relate his colours to other (usually tactile) images (as damask, verdurous, Tyrian, rubious, argent), a tendency still more evident with other colourists such as Francis Thompson and Gerard Hopkins.

P. Trevor-Roper

*The World Through Blunted Sight*

New York, Bobbs-Merrill, 1970

# ABSTRACT DEPARTMENT

EDITED BY DAVID SHOCH, M.D.

## ACTA OPHTHALMOLOGICA

PUPILLARY FLOW IN THE WATER PROVOCATION TEST. Wiebert, O. (University Eye Clinic, Lund, Sweden), Acta Ophth. 49: 317-327, 1971.

The author measured the flow of aqueous into the anterior chamber by examination of the bubble of aqueous which appears over the edge of the pupil in an aqueous tinged with fluorescein. The bubbles were photographed and a calculation of flow made from them. The author found that the water provocative test increases the pupillary flow by about 50%. This increased flow remains for at least 90 minutes, a time when the intraocular pressure is already normalized. (4 figures, 5 tables, 8 references)—David Shoch

OCCLUSION OF THE CENTRAL RETINAL ARTERY AND RETINAL BRANCH ARTERIOLES. Karjalainen, K. (University of Helsinki, Finland), Acta Ophth. Suppl. 109:9-96, 1971.

The author was able to follow 91 patients after central retinal artery or branch artery occlusion. After occlusion of the central retinal artery, 58% of the eyes were blind. However, fluorescein angiography revealed that recanalization of the retinal arteries occurred in all cases. The incidence of open angle glaucoma in patients with retinal arterial occlusion was 5%. Therefore, the author feels that glaucoma is not of etiologic significance in the development of retinal arterial occlusion. On the other hand, the incidence of neovascular glaucoma after occlusion was 2%. None of these patients exhibited open angle glaucoma of the opposite eye. Of the nine patients with neovascular glaucoma, three had diabetes and one had an aneurysm of the ipsilateral internal carotid artery. (38 figures, 18 tables, 109 references)—David Shoch

## ANAESTHESIA

PHENOPERIDINE AND DROPERIDOL AS PREMEDICANTS. A CONTROLLED STUDY IN OPHTHALMIC SURGICAL PROCEDURES IN COMBINATION WITH RETROBULBAR BLOCK. Steele, P. R. and Masheter, H. C. (Bristol Eye Hospital, England), Anaesthesia 26: 311-317, July, 1971.

Four different regimes to provide sedation and analgesia in patients undergoing ophthalmic surgery under local analgesia with retrobulbar block have been assessed under double blind conditions. The results showed that droperidol 5 mg and phenergan 25 mg intramuscularly one hour before operation followed by a further 5 mg droperidol plus phenoperidine 0.5 mg intravenously five minutes before retrobulbar block gave the best sedation and postoperative state. A significantly greater incidence of amnesia (33%) was associated with this combination compared with pethidine 50 mg and phenergan 25 mg given intramuscularly. (2 figures, 2 tables, 3 references)—Authors' abstract

## ARCHIV FÜR DERMATOLOGISCHE FORSCHUNG

BASAL CELL NEVUS SYNDROME WITH RETINOPATHIA PIGMENTOSA, RECURRENT INTRAVITREOUS BLEEDING, AND CHROMOSOMAL ABERRATIONS. (German) Happle, R., Mehrle, G., Sander, L. Z. and Hohn, H. (Universitat Freiburg, Germany), Arch. Derm. Forsch. 241:96-114, 1971.

In a patient with various types of tumors (nevoid basal cell carcinoma, neurofibroma, fibroma of the buccal mucosa), skeletal anomalies and a family history of basal cell carcinoma and of other malignant diseases, the diagnosis of a "basal cell nevus syndrome" is proposed. In addition, the patient exhibited further pathological conditions hitherto unreported in basal cell nevus syndrome: retinopathia pigmentosa with complicated cataract on both eyes; recurrent intravitreous bleeding of the left eye; a high frequency of chromosomal breakage in lymphocyte and fibroblast cultures. A marker chromosome (C-group chromosome with satellites at the short arm) was found in fibroblast metaphases of the patient's daughter. (5 figures, 2 tables, 80 references)—Authors' abstract

## Archiv für Klinische und Experimentelle Ophthalmologie

APPEARANCE OF THE FLUORESCENCE OF THE OPTIC NERVE. II. ATROPHY OF THE OPTIC NERVE. (German) Baurmann H. and Wink, B. (Univ.-Augenklinik Bonn, Germany), Arch. Klin. Exp. Ophth. 182: 120-126, 1971.

The absence of coloring by fluorescein does not necessarily indicate avascularity. On the other hand, the presence of fluorescence does not reliably exclude an atrophy. Therefore, fluorescein angiography does not offer any real advantage in diagnosis of atrophy of the optic nerve head. (3 figures, 10 references)—David Shoch

PATHOLOGY OF SHORT PULSE RETINAL PHOTOCOAGULATIONS USING THE GOLDMANN CONTACT LENS. Marshall, J., Fankhauser, F., Lotmar, W. and Roulier, A (Institute of Ophthalmology, London), Arch. Klin. Exp. Ophth. 182:154-169, 1971.

The problem of hypercoagulation and the occurrence of postcoagulative maculopathy have long been associated with xenon arc photocoagulation procedures. The virtual absence of these complications with pulsed ruby laser coagulations has led many workers to experiment with short pulse exposure techniques. The authors show that both systems produce damage only in the outer retinal layer, and result in very similar scar formations, with no involvement of the inner plexiform or nerve fiber layers. (7 figures, 1 table, 22 references)—David Shoch

## Archives of Neurology

EYE MOVEMENTS DURING SLEEP. Jacobs, L., Feldman, M. and Bender, M. B. (Mount Sinai Hospital, 1 E. 100th St., New York 10029), Arch. Neurol. 25:151-159, Aug., 1971.

Eye movements were recorded by DC oculogram in eight normal subjects during 31 nights of sleep. A consistent series of ocular positional changes and movements occurred in every subject. Initially, eyelid closure induced upward movement of the globes. The eyes then remained elevated during 55% to 85% of the time spent in stages 2, 3, and 4. With the onset of stage of rapid eye movement, the eyes moved down abruptly to or below the central position. Movements during this stage were quite unlike waking eye movements but showed a similar pattern in every subject. These movements were 5% to 15% horizontal, 25% to 35% vertical, and 55% to 65% oblique. The movement sequences and the time intervals between movements were not random. The results suggest that during sleep there is a pattern of activity of the oculomotor system which is similar in every subject. (9 figures, 22 references)—Authors' abstract

## Archives of Ophthalmology

OCULAR CHANGES FOLLOWING AIR-BLAST INJURY. King, Y. Y. (University of Arkansas Medical Center, Little Rock, Ark.), Arch. Ophth. 86:125-126, Aug., 1971.

The air blast reported here came from an air hose at a gasoline service station. The air blast apparently perforated the conjunctiva and dissected along the lining of the optic nerve, down the sheath of the carotid artery into the mediastinum. Alternatively, the pneumomediastinum could have resulted from dissection along the cervical neck planes into the mediastinal area. The cause of the optic nerve atrophy was not evident; however, air compression or even optic nerve transection could have occurred. This case demonstrates the possible danger of a common source of air blast. (2 figures)—Author's abstract

LIGHT COAGULATION IN PRESUMED HISTOPLASMIC CHOROIDITIS. Watzke, R. C. and Leaverton, P. E. (University Hospitals, Iowa City 52240), Arch. Ophth. 86:127-132, Aug., 1971.

A controlled study was designed to evaluate light coagulation as treatment for presumed histoplasmic chorioretinitis. Twenty-nine patients were selected. Allocation of patients to a treatment or an untreated control group was made by using a table of random numbers. Results in the two groups were compared over a one-year observation period. The study was designed to minimize measurement and observation bias and the effect of interim remissions and exacerbations of the disease. The results indicate that this therapy is of no value in the long-term management of this disease. (2 fig-

tures, 5 tables, 7 references)—Authors' abstract

HYDROPHILIC CONTACT LENSES IN CORNEAL DISEASE. Takahashi, G. H. and Leibowitz, H. M. (University Hospital, 750 Harrison Ave., Boston 02118), Arch. Ophth. 86: 133-137, Aug., 1971.

Four patients suffering from chronic bullous keratopathy with minimal stromal scarring were fitted with a hydrophilic contact lens. The lens was worn continuously, 24 hours a day, and 5% sodium chloride drops were administered topically every two hours during the day. Two of the four patients experienced a satisfactory response to therapy manifested by decreased epithelial and stromal edema and improvement in visual acuity. Approximately two weeks of therapy were required before clinical improvement could be documented in successful cases. (2 figures, 9 references)—Authors' abstract

FLUOROMETHOLONE. Fairbairn, W. D. and Thorson, J. C. (Allergan Pharmaceuticals, 18600 Von Karman, Irvine, Calif. 92664), Arch. Ophth. 86:138-141, Aug., 1971.

Fluorometholone 0.1% ophthalmic suspension applied topically was found to be an effective treatment in 308 patients with mild to severe noninfectious inflammatory disorders of the eye. The effect of fluorometholone on intraocular pressure was examined in steroid reactors who had accurately documented histories of pressure responses to prednisolone, dexamethasone, or betamethasone. The drug was also tested in a relatively large random patient population, including many with glaucoma, whose intraocular pressures were observed. The results of these studies indicate that fluorometholone shows a substantially reduced tendency to increase intraocular pressure as compared to several other steroids used topically. (4 tables, 13 references)—Authors' abstract

ISCHEMIC RETINOPATHY DUE TO CARBON MONOXIDE POISONING. Bilchik, R. C., Muller-Bergh, H. A. and Freshman, M. E. (Washington University School of Medicine, 660 S. Euclid, St. Louis 63110), Arch. Ophth. 86:142-144, Aug., 1971.

A family of three, exposed chronically to high levels of carbon monoxide in their home, was hospitalized with nonspecific symptoms and physical findings limited to the eyes. Papilledema, retinal hemorrhages, and cotton wool exudates, all believed to reflect tissue ischemia, resolved spontaneously. (3 figures, 15 references)—Authors' abstract

OCCULT INTRAOCULAR PERFORATIONS FROM BROW AND LID LACERATIONS. Goldberg, M. F. and Tessler, H. H. (University of Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago), Arch. Ophth. 86: 145-149, Aug., 1971.

Minor brow and lid lacerations may be associated with scleral and retinal perforations, even when the lacerations are apparently remote from the globe. Reports of three cases in children have been used to illustrate that the classical signs of scleral perforation need not always be present. This appears especially true of injuries caused by narrow, sharp objects such as darts, scissors and knives. The necessity of suspecting perforation injuries to the globe cannot be over emphasized. (5 figures, 13 references)—Authors' abstract

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE). Landers, III, M. B. and Klintworth, G. K. (Duke University Medical Center, Durham, N. C. 27706), Arch. Ophth. 86:156-163, Aug., 1971.

This report describes for the first time the finding of microtubular structures, probably viral nucleocapsids, by electron microscopy within retinal lesions of a child with subacute sclerosing panencephalitis (SSPE), whose clinical illness began with visual impairment. The tubular structures within the retina were identical to those previously described in the brain tissue of patients with this disease. They were also seen in the cortical neurons and neuroglia of this case and were present in the cell cultures obtained from the frontal lobe at autopsy. A measles virus has now been isolated from the brain. These findings indicate that there is a direct invasion of the retina by the same pathogenic agent affecting the central nervous system. (10 figures, 22 references)—Authors' abstract

RESECTION OF THE FACIAL NERVE FOR BLEPHAROSPASM. Hathaway, H. K. (Medical Towers, 1000 E. Third St., Chatta-

nooga, Tenn.), Arch. Ophth. 86:178-181, Aug., 1971.

Essential blepharospasm is a progressive, involuntary, spasmodic closure of the eyelids. It is probably the result of a focal disturbance in the suppressor strip 4-S of Hines or the bulbar reticular formation. Nonsurgical measures have been found to be of little benefit except in the mildest cases. Alcohol injections have the disadvantage of being painful, have a high failure rate, and produce contraction of the soft tissue. The most effective and long lasting relief seems to be obtained by selective neurectomy of the facial nerve. The technique is based on exposing the main trunk of the facial nerve and serially avulsing the temporal, zygomatic and buccal branches of the nerve. With the aid of a nerve stimulator, the completeness of the peripheral denervation can be determined and special attention focused on the variable buccal branch of the facial nerve. The skin incision used gives an excellent cosmetic result and allows for wide exposure of the main trunk and the branches of the facial nerve to be avulsed. The altered facial expression which follows the operation is less noticeable than the constant blinking. Exposure keratitis has not developed as so often happens after Bell's palsy. (4 figures, 15 references)—Author's abstract

EXPERIMENTAL CYANIDE OPTIC NEUROPATHY. Lessell, S. (Boston University School of Medicine, Boston, Mass.), Arch. Ophth. 86:194-204, Aug., 1971.

Sodium cyanide intoxication of rats produced demyelinative and necrotic lesions in the corpora callosa in 70% and the optic nerves in 20%. The optic neuropathy was bilateral, focal and retrobulbar. All animals with optic neuropathies had marked callosal lesions. Chiasmal involvement was rare. Since callosal lesions are extremely rare in a patient with optic atrophy and since the corpora callosa seem to be particularly sensitive to cyanide, it appears unlikely that cyanide is responsible for human optic nerve diseases. (10 figures, 25 references)—David Shoch

## ARCHIVES OF PATHOLOGY

OPHTHALMIC COCCIDIOIDOMYCOSIS. Olavarria, R. and Fajardo, L. F. (Stanford University School of Medicine, Palo Alto, Calif.), Arch. Path. 92:191-195, Sept., 1971.

A case of disseminated coccidioidomycosis with bilateral involvement of choroid and optic nerves is described. Miliary choroid granulomas probably resulted from coccidioidal endocarditis of mitral valve. A secondary source of hematogenous dissemination was found in a branch of the hepatic vein. Arthrospores, as well as sporangia, were demonstrated in the latter. (5 figures, 14 references)—Authors' abstract

## BRITISH JOURNAL OF OPHTHALMOLOGY

RUBEOSIS OF THE IRIS AND HEMORRHAGIC GLAUCOMA IN PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY. Madsen, P. H. (University Hospital, Arhus, Denmark), Brit. J. Ophth. 55:368-371, June, 1971.

Rubeosis of the iris is relatively frequent in eyes with proliferative diabetic retinopathy and occurred in 43% in the author's series (58 eyes). Fourteen of these eyes developed hemorrhagic glaucoma. Included in this series are 22 patients who had been subjected to hypophysectomy. (1 figure, 3 tables, 9 references)—David Shoch

PROGNOSIS FOR VISION AND FUNDUS CHANGES IN PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY. Madsen, P. H. (University Hospital, Arhus, Denmark), Brit. J. Ophth. 55:373-383, June, 1971.

Sixty-eight patients with proliferative diabetic retinopathy were followed for from 7 to 131 months. At the end of this time, 49 had retained visual acuity of 0.3 in one or both eyes. Progression of the proliferative retinopathy was observed in nearly one-half the eyes, in both hypophysectomized and non-hypophysectomized patients. Hypophysectomy seems to postpone the aggravation of fundus lesions but strict clinical studies are required to prove or disprove this apparent tendency. (11 figures, 9 tables, 17 references)—David Shoch

IRIDOCYCLO-RETRACTION IN NARROW-ANGLE GLAUCOMA. Krasnov, M. M. (Second Medical Institute, Moscow, USSR), Brit. J. Ophth. 55:389-395, June, 1971.

A new surgical procedure (iridocyclo-retraction) has been developed for narrow-angle

glaucoma, especially in cases with synechial iris closure. The iris root is forced back from the filtering zone and kept back by two (sometimes three) interposing autoimplants of scleral tissue. The operation has been successfully tried in 141 cases during a 3-year period. Experiments on rabbits have shown the method to be based on sound principles. Iridocyclo-retraction has substantial advantages over iridectomy and iridencleisis and deserves a wider clinical use. (4 figures, 1 table, 4 references)—Author's abstract

COLOBOMATOUS CUPPING OF THE OPTIC DISC. Rintoul, A. J. (Royal Naval Hospital, Haslar, Gosport, Hants), Brit. J. Ophth. 55:396-399, June, 1971.

Congenital colobomas of the optic nerve head may be mistaken for glaucomatous cupping. The author reports a patient with bilateral colobomas who had a loss of the superior field in the right eye and a typical Bjerrum scotoma in the left. Differential diagnosis from glaucoma was based on the fact that the intraocular pressure was normal and that the field defects were non-progressive. It is important to differentiate these congenital colobomas from glaucoma in order to avoid needless treatment to the patient. (4 figures, 30 references)—David Shoch

## CANADIAN JOURNAL OF OPHTHALMOLOGY

THE HYDROPHILIC (HYDRON) CORNEOSCLERAL LENS IN THE TREATMENT OF CORNEAL DISEASE. Lerman, S. and Sapp, G. (Royal Victoria Hospital and McGill University, Montreal, Canada), Canad. J. Ophth. 6: 1-8, Jan., 1971.

The hydrophilic (Hydron) corneoscleral lens has been employed in the therapy of bullous keratopathy. The possibility that ocular preservatives such as benzalkonium chloride and chlorbutanol might concentrate within these lenses was investigated. These studies showed that this did not occur to any significant extent and the patients were thus able to use whatever ocular medications they required (e.g. antiglaucoma drops) while wearing the lenses. The lens was worn for 24 hour periods, then removed, rinsed and boiled for 10 to 15 minutes in physiological saline, cooled and re-inserted. The majority of the patients obtained rapid and complete relief from their signs and symptoms and have been wearing the lenses for many months. (2 figures, 5 tables, 3 references)—Authors' abstract

THE DOSE RESPONSE OF HUMAN INTRAOCULAR PRESSURE TO PILOCARPINE. Drance, S. M. and Nash, P. A. (University of British Columbia, 2550 Willow St., Vancouver, Canada), Canad. J. Ophth. 6:9-13, Jan., 1971.

The effect of single dose instillations of 1%, 2%, 4% and 8% pilocarpine into one eye of 12 ocular hypertensive patients was studied. It was shown that maximal pressure reduction occurred two hours after the instillation of the single dose and was dose related up to 4% pilocarpine. The duration of 8% pilocarpine was considerably longer and at eight hours following the instillation of a single dose, the dose relationship showed that the 8% pilocarpine retained its maximal pressure reducing qualities for that period of time. (6 figures, 5 references)—Authors' abstract

SIMULATED SUSTAINED RELEASE PILOCARPINE THERAPY AND AQUEOUS HUMOR DYNAMICS. Lerman, S. and Reininger, B. (McGill University, Montreal, Canada), Canad. J. Ophth. 6:14-23, Jan., 1971.

A study was performed in which a simulated form of sustained release pilocarpine therapy was compared with the conventional method of pilocarpine therapy in a series of patients with open angle glaucoma. The results indicate that if a suitable method of prolonged release pilocarpine therapy could be developed, then most patients with open angle glaucoma would require a total 24 hour dose of pilocarpine hydrochloride which would be between 10 and 25 times less than the therapy the patient is presently using. This form of pilocarpine therapy would also have the advantage of maintaining continuous control of intraocular pressure both during the day and night. Since the total concentration of pilocarpine required would be so markedly diminished, it would be of value in those patients who display extreme sensitivity to cholinergic drops. (8 tables, 4 references)—Authors' abstract

VASCULAR FACTORS IN ASTEROID HYALOPATHY. Lamba, P. A. and Shukla, K. N. (Jawaharlal Institute of Postgraduate Medical Education, Pondicherry-6, India), Canad. J. Ophth. 6:46-51, Jan., 1971.

Thirty patients with asteroid bodies in the vitreous have been clinically and biochemically evaluated to determine the association with diabetes mellitus, hypercholesterolemia and hypertension. A significant number of cases were seen to be associated with diabetes, hypertension and evidence of angiosclerosis. It is suggested that vascular changes due to the associated above conditions may play a significant role in altering the permeability of the vessels and the deposition of the asteroid bodies in the vitreous. (5 tables, 17 references)—Authors' abstract

CYTOLOGY OF THE ANTERIOR CHAMBER FLUID IN EYES WITH CORNEAL XENOGRAFTS. Fowlder, J. H. and Basu, P. K. (1 Spadina Crescent, Toronto 179, Canada), Canad. J. Ophth. 6:68-71, Jan., 1971.

Millipore filters have been employed to examine the cytology of the anterior chamber fluid in xenografted and unoperated rabbit eyes and to quantitate the effects of a topical steroid in grafted eyes. The concentration of cells in the aqueous humor of grafted eyes increased to several hundred times that found in unoperated control eyes, during the second and third postoperative weeks. When topical steroids were administered in the third week postoperatively, the aqueous cellular response was reduced to control levels. (1 figure, 8 references)—Authors' abstract

CICATRICIAL ECTROPION IN EPIDERMOLYSIS BULLOSA AND IN CONGENITAL ICHTHYOSIS: ITS PLASTIC REPAIR. Hill, J. C. and Rodrigue, D. (Toronto General Hospital, Toronto, Canada), Canad. J. Ophth. 6: 89-97, Apr., 1971.

The ectropion that occurs in these two diseases is extremely severe and frequently results in the loss of the eye from exposure. The authors point out that the only effective type of repair is free skin grafting since in both these conditions there is a loss of tissue. However, grafting alone is insufficient since the ectropion almost always returns. It is necessary to put in permanent lid adhesions to prevent the recurrence of the ectropion. They point out that patients frequently will demand release of the adhesions but to do so is to invite a return of the ectropion. (14 figures, 8 references)—David Shoch

THE CONTROL OF CORNEAL GRAFT REACTION BY TOPICAL APPLICATION OF ANTIMITOTIC AGENTS (THIO-TEPA AND COLCHICINE): Akinosho, E. A. and Basu, P. K. (University of Toronto, 1 Spadina Crescent, Toronto, Canada), Canad. J. Ophth. 6: 109-114, Apr., 1971.

The effects of two antimitotic agents, Thiotepa and colchicine, on the corneal xenograft reaction in rabbits, were studied. These agents showed an inhibitory action on the vascularization and cellular infiltration of the graft. In the dosage used, colchicine appeared to be slightly less effective than Thio-tepa. (6 figures, 2 tables, 6 references)—Authors' abstract

THE CHANGES IN THE BLOOD SUPPLY OF THE POSTERIOR POLE OF RABBITS WITH OCULAR HYPERTENSION. de Freitas, F. and Morin, J. D. (University of Toronto, 1 Spadina Crescent, Toronto, Canada), Canad. J. Ophth. 6:139-142, Apr., 1970.

Thirty-five albino rabbits were made glaucomatous for one week by injecting methyl cellulose into the anterior chamber. In all the glaucomatous eyes, there was a filling defect in the peripapillary chorodial vessels supplied by the analogue of the circle of Zinn. Furthermore, there was narrowing and obliteration of the central retinal artery which was more easily seen in the latex injected specimens. Cupping was seen in 50% of the specimens. (5 figures, 9 references)—Authors' abstract

IMMUNOSUPPRESSION AND KERATOPLASTY. McCulloch, C. (Toronto General Hospital, Toronto, Canada), Canad. J. Ophth. 6: 161-169, July, 1971.

Graft rejection may involve the entire graft or may involve only one of its layers. The author feels that one might have epithelial rejection, stromal rejection or endothelial rejection without involvement of the whole graft. He describes seven cases in which graft rejection began and in these seven azathioprine was used. In one case the course of rejection was not affected but in the other six, improvement occurred with the use of the drug. For mild rejections, atropine and local steroids may be sufficient but with more severe rejections the author advises the use of immunosuppressive agents. (7 figures, 1 table, 23 references)—David Shoch

A NEW TREATMENT FOR "A" AND "V" PATTERNS IN STRABISMUS BY SLANTING MUS-

CLE INSERTIONS. Boyd, T. A. S., Leitch, G. T. and Budd, G. E. (University of Alberta Hospital, Edmonton 61, Canada), Canad. J. Ophth. 6:170-177, July, 1971.

In addition to the usual recession or resection in cases of A and V strabismus, the authors also recess one border of the muscle more than another. In V exotropia for example, the superior border is recessed more than the inferior border. In V esotropia on the other hand, the inferior border is recessed more than the upper. The authors' patients were compared with a group in which only horizontal surgery was done and there was a clear superiority for their method. (8 figures, 6 tables, 7 references)—David Shoch

## Clinical Science

GENETIC INFLUENCES IN DRUG RESPONSES OF THE EYE AND THE HEART. Bertler, A. and Smith, S. E. (Dept. of Pharmacology, Lund University, Lund, Sweden), Clin. Sci. 40:403-410, May, 1971.

Pupillary responses to locally applied phenylephrine and cardiac responses to intravenous hyoscine N-butylbromide have been studied in ten pairs each of healthy monovular and binovular twins aged between 24 and 60 years. Under identical lighting conditions resting pupil diameters differed widely among individuals, being greater in female subjects and in those with larger irides and smaller with increasing age. Monovular twins, but not binovular twins, showed significant concordance in iris diameter, initial pupil diameter, initial heart rate and responses to both drugs. The results suggest that these responses were dependent on the concordance of peripheral sympathetic and parasympathetic tone within each twin pair. It is concluded that much of the variability in response to drugs acting on the autonomic nervous system is determined by physiological factors and that these are genetically influenced. (2 figures, 2 tables, 18 references)—Authors' abstract

## International Ophthalmology Clinics

TUMORS INVOLVING THE ORBITAL REGION. Smith, B. (Manhattan Eye, Ear and Throat Hospital, New York), Int. Ophth. Clin. 10:3-10, 1970.

Various tumors of the lids and orbit are reviewed and the author outlines the appropriate surgical therapy. He concludes that the most common complication of surgical treatment of tumors around the eye is the failure to execute radical or complete extirpation of the entire neoplasm at the initial operation. Conservative, that is, incomplete resection results from the surgeon's failure to create a sufficient tissue defect because he is timid or uninformed concerning the proper methods of closing the defect created by surgical eradication of the tumor. Although post-surgical complications such as trichiasis, entropion, ectropion, etc. may occur these can usually be rectified by competent secondary surgery.—David Shoch

CONGENITAL AND SURGICAL ANOPHTHALMIA. Spaeth, E. B. (Wills Eye Hospital, Philadelphia, Penn.), Int. Ophth. Clin. 10:11-21, 1970.

In congenital anophthalmia the first procedure necessary is a subconjunctival implantation of a gold ball into the socket, usually through the lower lid. The second procedure should be a creation of superior and inferior cul-de-sacs which in infants must usually be constructed from skin grafts since there is not sufficient mucous membrane available. Thirdly, metal or plastic conformers should be used and gradually increased as the child's face grows until a satisfactory prothesis can be fitted and worn. (7 figures)—David Shoch

EPIPHORA AND RELATED DISORDERS OF THE LACRIMAL SYSTEM. Cherubini, T. D. (Manhattan Eye, Ear and Throat Hospital, New York), Int. Ophth. Clin. 10: 23-22, 1970.

The author feels that where possible, reconstruction of the lacrimal system is the treatment of choice for most problems. The only real indication for dacryocystectomy is the presence of a tumor. Further, he feels that surgery is indicated even in the presence of an acutely inflamed dacryocystitis. Establishment of an open system and the use of postoperative antibiotics cure the infection without incident. —David Shoch

ECTROPION AND ENTROPION. Silver, B. (Washington University School of Medicine, St. Louis, Missouri), Int. Ophth. Clin. 10:33-45, 1970.

For ordinary senile entropion the author feels that the excision of a base down triangle of tarsus gives the best result. On the other

hand the most definitive operation is a modified Wheeler orbicularis transplant. For cicatricial disease, generally freeing of the scars is necessary with insertion of a skin graft. Since grafts tend to shrink, it is particularly important to overcorrect a cicatricial ectropion. (11 figures, 5 references)—David Shoch

BAGGY LIDS. Beyer, C. K. (Massachusetts Eye and Ear Infirmary, Boston, Mass.), Int. Ophth. Clin. 10:47-53, 1970.

The most important point in correction of baggy lids is conservatism. Ectropion is very difficult to correct and undercorrection is preferable to overcorrection. This is particularly true for the lower lids. Further, meticulous hemostasis is essential to avoid postoperative hematomas and disruption of the desired result. (3 figures, 14 references)—David Shoch

TRAUMA AND BURNS. Tenzel, R. R. (Bascom Palmer Eye Institute, Miami, Florida), Int. Ophth. Clin. 10:55-69, 1970.

An important point the author makes is that for trauma to the orbit it is essential that a Water's view be ordered. Routine skull films do not reveal orbital fractures. For chemical burns, the most important thing is irrigation. The author advises inserting an intravenous type catheter through the skin of the lid into the inferior cul-de-sac. The end of the Intracath tubing is pulled out from the cul-de-sac and flamed with a match which causes flanging of the end of the tube. This is pulled back until the tube is just in the cul-de-sac and through this tubing a continuing irrigation of balanced salt solution mixed with an antibiotic can be dripped round the clock. (12 figures)—David Shoch

ENDOCRINE EXOPHTHALMOS. Wilkins, R. B. and Sessions, R. B. (Hermann Hospital, Houston, Texas), Int. Ophth. Clin. 10:71-84, 1970.

A distinction should be made between the ocular manifestations of thyrotoxicosis and endocrine exophthalmos, which are only indirectly related. Endocrine exophthalmos is a functionally and cosmetically treatable condition. The preoperative evaluation must rule out conditions not treated by decompression. The otorhinolaryngologist and ophthalmologist, with a combined approach, are best equipped to evaluate, treat, and follow these patients. The transantral orbital decompression is the surgical procedure of choice. (6 figures, 24 references)—Authors' abstract

THE SURGICAL APPROACH TO ENDOCRINE OPHTHALMOLOGY. Langham, III, J. E. (University of California Medical Center, San Francisco, Calif.), Int. Ophth. Clin. 10:85-95, 1970.

Each of the complications of endocrine ophthalmopathy is presented and appropriate therapy discussed. For lid retraction, the best treatment is separation of the levator from the upper border of the tarsus. Occasionally only the involuntary levator should be separated but in most cases it is necessary to separate the attachments of the voluntary aponeurosis as well. For muscle problems the appropriate therapy is recession of the restricted muscle with freeing of any adhesions, if present. Finally, for cases that need decompression of the orbit, the author advises an antral decompression. (15 references)—David Shoch

BLEPHAROPTOSIS: CLINICAL EVALUATION AND THERAPEUTIC RATIONALE. Beard, C. (University of California Medical School, San Francisco, Calif.), Int. Ophth. Clin. 10:97-115, 1970.

Examination of a patient with ptosis is outlined and appropriate therapy for mild, moderate and severe ptosis is given. Very specific recommendations are made for the type of surgery to be done and for the amount of surgery in each of these three divisions. The author feels that whenever possible the operation of choice is a levator muscle resection. (5 figures, 20 references)—David Shoch

LEVATOR RESECTION FOR MINIMAL PTOSIS. Fasanella, R. M. and Servat, J. (Yale-New Haven Medical Center, New Haven, Conn.), Int. Ophth. Clin. 10:117-130, 1970.

For patients with a minimal ptosis, that is, not more than 1.5 to 2 mm, who have a good lid fold, the authors advise a block resection which is done by simply grasping the upper edge of the tarsus and the conjunctiva and the levator between two curved hemostats. The tissue is excised and the defect closed with either silk or cat gut. This block resection appears to give a good cosmetic and functional result in cases with minimal ptosis. (12 figures, 8 references)—David Shoch

THERAPEUTIC CONTACT LENSES. Gould, H. L. (Manhattan Eye, Ear and Throat Hospital, New York), Int. Ophth. Clin. 10:131-141, 1970.

The most dramatic indication for the use of a flush-fitting shell is painful bullous keratopathy. The pain is relieved completely within a few days of insertion of the shell. In some cases an optical modification can be made which gives the patient reasonable vision. A second important use for flush-fitting shells is in the treatment of Stevens-Johnson syndrome. Finally, the custom molded shell is ideal as a cosmetic cover over a disfigured globe. (6 figures, 8 references)—David Shoch

THE PREPARATION OF METHYL METHACRYLATE IMPLANTS FOR REPAIR OF ORBITAL FRACTURES. Miller, G. R. (University of Miami School of Medicine, Miami, Florida), Int. Ophth. Clin. 10:143-144, 1970.

The technique for molding an implant at surgery is described, but the author advises that the use of premolded, flat, thin plates saves time and avoids the heat generated during polymerization in vivo. Wiring of the plate to the rim in acute fractures is not necessary. (1 reference)—David Shoch

THE PALPEBRAL SPRING FOR PARALYSIS OF THE UPPER EYELID. Guy, C. L. and Ransohoff, J. (University Hospital, New York), Int. Ophth. Clin. 10:145-151, 1970.

The palpebral spring is used for patients who have had complete or transient paralysis of the facial nerve and are unable to close the involved eye. The spring is fashioned so that on relaxation of the levator, it passively closes the upper eye lid yet allows the levator to overcome the power of the spring and open the eye at will. Twenty-four such springs were inserted and of these 19 are still in place and appear to be working well. (3 figures, 4 references)—David Shoch

## INVESTIGATIVE OPHTHALMOLOGY

THE EFFECT OF HYPERBARIC OXYGENATION ON RETINAL ISCHEMIA. Flower, R. W. and Patz, A. (Applied Physics Laboratory, 8621 Georgia Ave., Silver Spring, Md. 20910), Invest. Ophth. 10:605-616, Aug., 1971.

Retinal circulation was occluded by direct burning of the arterioles with an argon laser. In a second group of experiments the retinal circulation was occluded by increasing intraocular pressure but this also decreased the choroidal blood flow. The viability of the retina following these occlusions was measured by noting the amplitude of the ERG. This is a reliable and a sensitive indicator of viability of the retinal layers. Results indicate that hyperbaric oxygen significantly increases the range of oxygen diffusion from the choroid to supply ischemic inner retinal layers following retinal arterial occlusion. To be effective, oxygen therapy must be administered under hyperbaric pressures. Breathing 100% oxygen at sea level pressure produced little or no protection for ischemic inner retinal layers. (6 figures, 15 references)—David Shoch

## JOURNAL OF PEDIATRICS

NORRIE'S DISEASE: AN X-LINKED SYNDROME OF RETINAL MALFORMATION, MENTAL RETARDATION, AND DEAFNESS. Holmes, L. B. (Genetics Unit, Massachusetts General Hospital, Fruit St., Boston, Mass.), J. Pediatrics 79:89-92, July, 1971.

A family is reported in which six males in four generations had Norrie's disease, an X-linked recessive syndrome of retinal malformation, deafness, and mental retardation. It would seem that this disease may be frequently misdiagnosed as retrolental fibroplasia, retinoblastoma, retinal pseudoglioma, or congenital toxoplasmosis. Although this is only the third reported American family, it is likely that this disease will be more frequently recognized once it is better known. (2 figures, 10 references)—Author's abstract

CYCLOPENTOLATE (CYCLOGYL) TOXICITY IN PEDIATRIC PATIENTS. Adcock, III, E. W. (Fitzsimmons General Hospital, Denver, Colo. 80240), J. Pediatrics 79:127-129, July, 1971.

A 4½-year-old white male developed a generalized postganglionic cholinergic blockade after receiving six drops of 2.0% Cyclogyl over a period of one-half hour. (14 references)—Joel G. Sacks

THE CEREBRORETINAL DEGENERATIONS. Menkes, J. H., Andrews, J. M. and Can-

cilla, P. A. (UCLA Center for the Health Sciences, Los Angeles, Calif. 90024), J. Pediatrics 79:183-196, Aug., 1971.

An excellent article that tabulates the lipid storage diseases. The authors divide these into three groups: those without marked visceromegaly (Tay-Sachs, Batten-Bielschowsky); those with marked visceromegaly (Gaucher's, Niemann-Pick) and those with white matter degeneration (metachromatic leukodystrophy). The clinical characteristics of each entity are listed and where known, the enzymatic defect. (8 figures, 2 tables, 62 references)—David Shoch

ULTRASTRUCTURAL STUDIES IN LATE-ONSET AMAUROTIC IDIOCY: LYMPHOCYTE INCLUSIONS AS A DIAGNOSTIC MARKER Witzleben, C. L., Smith, K., Nelson, J. S., Monteleone, P. L. and Livingston, D. (Cardinal Glennon Memorial Hospital, 1465 Grand Blvd., St. Louis, Mo. 63104), J. Pediatrics 79: 285-293, Aug., 1971.

Light and electron microscopic studies have been carried out on brain and white blood cells from a patient with juvenile amaurotic idiocy. A variety of lipid inclusion, including both "multilamellar cytosomes" and "fingerprint" inclusions, were present in the brain, suggesting that these two morphologic types of inclusions may not always define separate metabolic disorders. In the lymphocytes, ultrastructurally striking lamellar cytoplasmic inclusions were found. Such inclusions have not previously been described in this disorder. The demonstration of these inclusions by electron microscopy may prove to be a distinctive and relatively simple diagnostic marker of the disease, or at least of the "type" of late-onset amaurotic idiocy present in this patient. (6 figures, 14 references)—Authors' abstract

## JOURNAL OF PEDIATRIC OPHTHALMOLOGY

CONGENITAL ESOTROPIA: DEFINITION, COURSE AND MANAGEMENT. Romano, P. E. (Children's Memorial Hospital, Chicago, Illinois), J. Pediat. Ophth. 8:38-92, May, 1971.

The term congenital esotropia should be reserved for those children with an esodeviation who have never had an opportunity for normal binocular vision. In clinical terms, any child with a proven constant esodeviation at four months of age should be considered to have congenital esotropia. This condition is hereditary but otherwise of unknown etiology. It is typically characterized by a large deviation, cross fixation and limited abduction bilaterally. There is, in addition, an apparent congenital defect for central fusion and the best functional result which can be obtained is a monofixation syndrome, microtropia, or microstrabismus. Although less than perfect, such a result is desirable because it is stable and is accompanied by a fair degree of binocular cooperation. Management starts with early and accurate diagnosis and early treatment of amblyopia to establish alternating or cross fixation. To obtain maximal function results, surgical correction of the deviation should be completed by age two to two and a half. Earlier surgery will not produce better functional results but may be indicated for cosmetic reasons. (11 references)—Author's abstract

TENDON TRANSPLANTATIONS FOR LATERAL RECTUS PARALYSIS. Billet, E. (Bronx Eye Infirmary, Bronx, New York), J. Pediat. Ophth. 8:102-104, May, 1971.

Four cases of congenital lateral rectus paralysis showed no improvement in abduction after temporal tendon transplantation of the vertical recti. Many favorable results in the literature following the Hummelsheim operation or one of its many modifications were cases of traumatic as opposed to congenital lateral rectus paresis. It is considered that traumatic paresis may improve even with simple horizontal muscle surgery, particularly the weakening of a contractured antagonist. Combined surgery, i.e., the one-stage horizontal and vertical operation, may have an additive effect which cannot be accomplished with these same procedures in two stages. However, the occasional severe postoperative complications from four rectus muscle surgery should preclude this operation. (19 references)—Author's abstract

## KLINISCHE MONATSBLÄTTER FÜR AUGENHEILKUNDE

RESULTS OF PROPHYLACTIC CRYORETINOPEXY. (German) Boke, W. and Voigt, G. (Univ.-Augenklinik Kiel, Germany), Klin. Mbl. Augenh. 159:12-21, July, 1971.

Ninety-eight patients (108 eyes), who had been treated prophylactically with low temperatures (cryoretinopexy), for retinal detachment were followed for two months to three years after the operation. Statistical data on the kind and distribution of the retinal degeneration are reported. Altogether, serious complications arose in three of the 108 eyes (detachment of the retina in two, and intraocular bleeding in one) of which two were relieved without sequelae. The complication rate is therefore by no means higher, but apparently lower than with prophylactic diathermy or photocoagulation. (1 figure, 6 tables, 62 references)—David Shoch

TRAUMATIC DAMAGE OF THE OPTIC NERVE. (German) Schmaltz, B. and Schurmann, K. (Klinik der Univ. Mainz, Germany), Klin. Mbl. Augenh. 159:33-51, July, 1971.

Over a 14 year period the authors treated 250 patients with craniocerebral injuries. Among these there were 13 cases of posttraumatic blindness. Nine of these had a primary complete loss of vision and in none of these was there any return of vision following decompression of the optic nerve. There were four cases where the visual deterioration occurred later; in only one of these was there a return of vision. Therefore, in general the authors counsel against decompression of the optic nerve in cases of traumatic injury. (2 figures, 91 references)—David Shoch

## LANCET

HIGH FREQUENCY OF DIABETES MELLITUS IN YOUNG ADULTS WITH CONGENITAL RUBELLA. Forrest, J. M., Menser, M. A. and Burgess, J. A. (Royal Alexandra Hospital for Children, Sydney, Australia), Lancet 2:332-334, 1971.

In 1967, fifty young adults with congenital rubella were reviewed. Diabetes mellitus was detected in one of the fifty patients. Subsequently four other patients with congenital rubella and diabetes mellitus were found from other sources. The original group of fifty young adults was then reassessed, with special attention to the detection of diabetes mellitus. Of forty-four patients available for review, five (including the original patient) had diabetic glucose-tolerance tests, and a further four had slight abnormalities in glucose tolerance together with abnormal insulin responses suggestive of latent diabetes mellitus. The combined incidence of diabetes and latent diabetes in this group of patients was nine out of forty-four (20%). These findings suggest a causative relationship between congenital rubella infection and diabetes mellitus. (3 tables, 23 references)—Authors' abstract

## PROCEEDINGS OF THE ROYAL SOCIETY OF MEDICINE

RETINAL PHOTOGRAPHY IN PREMATURE INFANTS: FORME FRUSTE RETROLENTAL FIBROPLASIA. Baum, J. D. (Institute of Child Health, Hammersmith Hospital, London), Proc. Royal Soc. Med. 64:777-779, July, 1971.

Ophthalmoscopy is no replacement for direct frequent arterial $Po_2$ measurement in premature infants receiving oxygen. In the infants at greatest risk of oxygen toxicity to the eye, those of less than 32 weeks gestation, the retina is not clearly visible because of the persistent tunica vasculosa lentis. Even if it were, the services of an expert ophthalmologist would be required every few hours, day and night, and even then he would be looking for a sign which probably points to established retinal damage. The finding of tortuous retinal arteries in surviving contemporary premature infants in whom oxygen thereapy has been given in the most carefully monitored fashion serves as a reminder that the limits of safety in prescribing an oxygen-enriched environment for premature infants are very narrow indeed. (2 figures, 1 table, 10 references)—Author's abstract

# NEWS ITEMS

EDITED BY THOMAS CHALKLEY, M.D.
*700 North Michigan Avenue, Chicago, Illinois 60611*

For adequate publicity, notices of postgraduate courses, meetings and lectures must be received *at least* three months prior to the date of occurrence.

### SEEING EYE OFFERS SCHOLARSHIPS

The Seeing Eye, Inc., Morristown, New Jersey, will make a few post-doctoral fellowships and medical school scholarships available to qualified candidates who wish to pursue a career in investigative ophthalmology. Details of this program may be obtained by writing to the Director of Grants, The Seeing Eye, Inc., Morristown, New Jersey 07960.

### RECENTLY DESCRIBED $CO_2$ LASER CALLED DANGEROUS

The 10-watt $CO_2$ laser described in the September issue of Scientific American is highly dangerous according to C. H. Knowles, President of Metrologic Instruments, Inc. He stated that its power is approximately 2000 times the safe level recommended by the Electronic Industries Association.

### POSTGRADUATE COURSE AND ALUMNI MEETING: WALTER REED ARMY MEDICAL CENTER

The fourth Walter Reed Ophthalmology Postgraduate Course and Alumni Meeting will be conducted at Sternberg Auditorium, Walter Reed Army Medical Center, Washington, D.C., on April 10-13, 1972. Speakers will include Alston Callahan, Harvey Thorpe, Thomas Walsh, Guillermo Pico, Arthur Linksz, Arthur Keeney, John Harris, Richard Lubow, Richard Richards, Mansour Armaly, Henry Allen, William Havener, and others, including alumni. There is no tuition fee, and advance registration is recommended but not mandatory.

For additional information contact Course Director Col. Budd Appleton, Box 4, OSC, Walter Reed General Hospital, Washington, D.C. 20012.

### CLINICAL CONFERENCE: WILLS EYE HOSPITAL

The 24th annual clinical conference of the Wills Eye Hospital will be held on February 3-5, 1972, at the Bellevue Stratford Hotel, Broad and Walnut Streets, Philadelphia, Pennsylvania. The Arthur J. Bedell Lecture will be given by Lorenz E. Zimmerman, Washington, D.C. There will be symposia on causes of failure in cataract surgery and how to avoid them, and on retinal vascular occlusive disease. Workshops will be held in plastic surgery, retinal diseases, refraction, motility, anesthesia, and neurology.

Inquiries should be addressed to Robert D. Mulberger, M.D., Chairman, Annual Clinical Conference Committee, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pennsylvania 19130.

### NEURO-OPHTHALMOLOGY COURSE: BASCOM PALMER EYE INSTITUTE

The ninth annual ophthalmology course of the Bascom Palmer Eye Institute at the University of Miami will be held January 4-7, 1972, at the Americana Hotel, Miami Beach, Florida. The first two days will be devoted to a basic course in neuro-ophthalmology aimed at the level of residence with no previous training. The final two days will be devoted to an advanced clinical seminar on genetics in ophthalmology.

The fee is $100 for practitioners and $40 for residents. Further information is available from the Neuro-ophthalmology Course, Inc., 11300 S.W. 179th Street, Miami, Florida 33157.

### CONTACT LENS COURSE: NEW ORLEANS ACADEMY OF OPHTHALMOLOGY

The New Orleans Academy of Ophthalmology and the Rudolph Ellender Medical Foundation have coordinated the 1972 programs concerning contact lenses. On April 8-9, 1972, the Ellender Eye Foundation will present a personalized instruction course in fitting techniques of hard and flexible lenses. The annual symposium of the New Orleans Academy of Ophthalmology will be held April 10-14, 1972. The lectures will include didactic material on all phases of medical contact lens practice and experience. The course will not duplicate materials. Guest speakers of the New Orleans Academy of Ophthalmology will include Chester J. Black, Jorge N. Buxton, Herber L. Gould, Peter Halberg, Herbert E. Kaufman, Ian Mackie, Perry Rosenthal, and Whitney G. Sampson.

### UNIVERSITY OF IOWA CLINICAL COURSE: ECHOGRAPHY OF THE GLOBE AND ORBIT

An intensive course for ophthalmologists and technicians in the performance of clinical echo-ophthalmography will be held at the Department of Ophthalmology in Iowa City May 8-10, 1972. The tuition for this course will be $150 for practicing physicians and $100 for residents.

For further information contact Karl Ossoinig, M.D., Department of Ophthalmology, University of Iowa Hospitals, Iowa City, Iowa 52240.

### CLINICAL SYMPOSIUM: ARKANSAS MEDICAL CENTER

The annual clinical symposium of the Department of Ophthalmology of the University of Arkansas Medical Center, will be held February 5-6, 1972. The session will be devoted primarily to dis-

cussion of current cases. Guest speakers include Henry L. Van Dyk and Thomas Acers.

Further information is available from Mrs. Lee Hallmark, Department of Ophthalmology, University of Arkansas Medical Center, Little Rock, Arkansas 72201.

### Corneal surgery course: Brooklyn Eye and Ear Hospital

A three-day course in surgery of the cornea will be given under the direction of A. Benedict Rizzuti and the staff of the Brooklyn Eye and Ear Hospital May 10-12, 1972. Surgical keratoplasty techniques will be demonstrated on patients. Special instrumentation, microscopic surgery, keratoprosthesis and related subjects will be discussed. Matriculants will perform corneal grafting procedures on animal eyes under supervision.

Tuition is $175, and the course is limited. Registration forms may be obtained from Mr. Vernon Dressler, Administrator, Brooklyn Eye and Ear Hospital, 29 Greene Avenue, Brooklyn, New York 11238.

### Ophthalmic radiology course: Columbia University

A postgraduate course in ophthalmic radiology will be presented by Columbia University, College of Physicians and Surgeons, under the direction of Guy D. Potter on Friday and Saturday, April 21 and 22, 1972. The course will deal with normal radiographic anatomy, tomography of the orbit and paranasal sinuses, congenital anomalies, the orbit in children including retinoblastoma, rhabdomyosarcoma, exophthalmos, orbital calcification, the sella turcica, trauma, foreign body localization, orbital contrast studies and orbital tumors. The faculty includes Jackson Coleman, William Cooper, Kenneth Dolan, Robert Ellsworth, Guy Potter, William Seaman, Michael Tenner, Patricia Tretter, Stephen Trokel, Galdino Valvassori, and Judah Zizmor. The course will be directed to ophthalmologists and radiologists.

For further information, please contact Dr. Guy D. Potter, Columbia-Presbyterian Medical Center, 622 West 168th Street, New York, New York 10032.

### Mid-winter Seminar: Colorado Ophthalmological Society

The mid-winter seminar sponsored by the Colorado Ophthalmological Society will be held in Snowmass-at-Aspen, January 31 through February 3, 1972. The speakers are Frederick C. Blodi, Arthur J. Jampolsky, Alex E. Krill, and Robert J. Brockhurst.

Further information is available from James M. Hersey, M.D., Colorado Ophthalmological Society, 1809 East 18th Avenue, Denver, Colorado 80218.

### Summer scholarships: Delta Gamma Foundation

Delta Gamma Foundation is offering summer scholarships for the training of orthoptists and teachers and consultants for visually handicapped children. Applicants are considered on individual merit and the amount of each grant depends on the cost of the specific training involved. Application deadline is March 15, 1972.

Further information may be obtained from Mrs. David Dunbar, 20 Elm Court, Anderson, Indiana 46011.

### Fight for Sight applications now being accepted

The Fight for Sight, founded in 1946 with the primary purpose of encouraging and financing eye research, has awarded $284,217 for the current year in support of basic and clinical research projects in ophthalmology and related sciences. Charles A. Perera, Chairman of the organization's Scientific Advisory Committee, stated that an intensive self-study of the research awards program of the Fight for Sight has resulted in a number of procedural changes, all designed to simplify application methods so that the administrative burdens might be eased for individual candidates, chiefs of departments, institutions and the Fight for Sight itself.

Applications for Fight for Sight fellowships and grants for the 1972–73 awards year are being accepted now and may be submitted until March 1, 1972. Requests for application forms should be directed to The Secretary, Fight for Sight, Inc., 41 West 57th Street, New York, New York 10019. Recipients of 1970–71 awards are as follows:

#### Grants-in-aid

| Investigator and Institution | Project title | Amount |
|---|---|---|
| Adams, Dr. Calvin K.<br>Willis, Dr. Richard D.<br>University of Florida<br>Gainesville, Florida | An animal model for prosthetic vision | $5,160 |
| Allansmith, Mathea, M.D.<br>Stanford University<br>Stanford, California | The etiology of corneal epithelial keratitis | 3,000 |

GRANTS-IN-AID

| INVESTIGATOR AND INSTITUTION | PROJECT TITLE | AMOUNT |
|---|---|---|
| Bigger, John F., M.D.<br>Washington University<br>St. Louis, Missouri | Steroid responsiveness in tissue culture fibroblasts | 5,295 |
| *Candia, Oscar A., M.D.<br>Mount Sinai School of Medicine<br>New York, New York | Electrolytes and water movement across isolated amphibia lens | 2,070 |
| Carr, Ronald E., M.D.<br>Siegel, Irwin M., Ph.D.<br>New York University<br>New York, New York | Ophthalmologic testing of tyrosinase positive and negative forms of generalized albinism: A pilot study | 1,820 |
| Cohen, Adolph I, Ph.D.<br>Washington University<br>St. Louis, Missouri | Role of the pigment epithelium in regulating the fluid volume of the subretinal space | 4,500 |
| Davidowitz, Jacob, Ph.D.<br>New York University<br>New York, New York | Osmic acid perfusion of extraocular muscle for correlated light and electron microscopy | 2,682 |
| *Dawson, William W., Ph.D.<br>University of Florida<br>Gainesville, Florida | Preliminary tests of a primate model for retinal pathology associated with chronically elevated intraocular pressure | 4,000 |
| Enoch, Jay M., Ph.D.<br>Washington University<br>St. Louis, Missouri | The application of the modulation transfer function test (of Fergus Campbell) to a clinical population | 4,500 |
| Eriksson, Aldur W., M.D.<br>Population Genetics Unit<br>Helsingfors, Finland | Continuation of studies on X-chromosomal retinoschisis in Finland | 6,240 |
| *Fischbarg, Jorge, M.D<br>Columbia University<br>New York, New York | The physiological role of the corneal endothelium in the preservation of the corneal transparency | 4,200 |
| *Forster, Richard K., M.D.<br>University of Miami<br>Bascom Palmer Eye Institute<br>Miami, Florida | Diagnosis and management of fusarium keratomycoses | 4,000 |
| Guvenc, Serpil, M.D.<br>Case Western Reserve University<br>Cleveland, Ohio | Development of a microcalorimetric device for the measurement of output power of ultrasonic diagnostic transducers | 9,175 |
| Henkind, Paul, M.D.<br>Albert Einstein College of Medicine<br>Bronx, New York | The embryology of the perimacular and peripapillary straight capillaries | 3,800 |
| *Holland, Monte, M.D.<br>Tulane University<br>School of Medicine<br>New Orleans, Louisiana | A clinical investigation of the effects of 6-hydroxydopamine in augmenting the adrenergic pressure-lowering response in the human glaucomatous eye | 2,000 |
| *Isa Abdallah M., Ph.D.<br>Meharry Medical College<br>Nashville, Tennessee | Characterization of antibodies to TRIC (Chlamydiae) agents | 5,000 |

GRANTS-IN-AID

| INVESTIGATOR AND INSTITUTION | PROJECT TITLE | AMOUNT |
|---|---|---|
| Kenyon, Kenneth R., M.D.<br>Johns Hopkins Hospital<br>Baltimore, Maryland | Ultrastructural studies in ocular pathology and development | 3,000 |
| Kobayashi, Shoji, M.D.<br>Retina Foundation<br>Boston, Massachusetts | Virus-induced embryonic gliomas of the retina | 5,977 |
| *Loeb, Gerald E.<br>The Johns Hopkins University<br>Baltimore, Maryland | Developmental work on a visual prosthesis | 4,500 |
| Maurice, David, Ph.D.<br>Stanford University<br>Stanford, California | Pressure relationships under the lids and under a contact lens | 3,500 |
| Nesburn, Anthony B., M.D.<br>Estelle Doheny Eye Foundation<br>Los Angeles, California | Experimental adenovirus infection of the rabbit eye | 7,150 |
| O'Rourke, J., M.D.<br>University of Connecticut Health Center<br>Hartford, Connecticut | Improved methods for study of uveoretinal uptake and distribution of radioactive zinc | 3,000 |
| Peyman, Gholam A., M.D.<br>University of Illinois<br>Chicago, Illinois | Peroxidase blood-brain barrier in the optic nerve | 1,750 |
| Podos, Steven M., M.D.<br>Washington University School of Medicine<br>St. Louis, Missouri | Cortisol suppression, diphenylhydantoin and primary open-angle glaucoma | 6,723 |
| Potts, Albert M., M.D.<br>University of Chicago<br>Chicago, Illinois | Exploration of machine-assisted diagnosis in ophthalmology | 5,950 |
| *Ripps, Harris, Ph.D.<br>New York University<br>New York, New York | The physiology of visual adaptation | 3,800 |
| Scott, Walter N., M.D.<br>Mount Sinai School of Medicine<br>New York, New York | Amino acid transport in the cornea | 4,615 |
| *Shakib, Manoucher, M.D.<br>New York University<br>New York, New York | Vitreo-retinal transport | 5,000 |
| Viernstein, Lawrence, Ph.D.<br>Pollack, Irvin P., M.D.<br>The Johns Hopkins University<br>Baltimore, Maryland | A proposal for the establishment of a laboratory for constant pressure applanation tonography | 6,732 |
| Witkovsky, Paul, Ph.D.<br>Columbia University<br>New York, New York | An anatomical and physiological investigation of the roof nucleus of the selachian brain | 4,783 |

## GRANTS-IN-AID

| INVESTIGATOR AND INSTITUTION | PROJECT TITLE | AMOUNT |
|---|---|---|
| *Woods, Wendell D., Ph.D.<br>Emory University<br>School of Medicine<br>Atlanta, Georgia | Metabolic systems in aqueous humor dynamics | 2,500 |
| Zwaan, Johan, M.D.<br>Children's Hospital Medical Center<br>Boston, Massachusetts | RNA synthesis by early lens cells | 6,000 |

## POSTDOCTORAL RESEARCH FELLOWSHIPS

| NAME AND INSTITUTION | DIRECT SUPERVISOR | PROJECT TITLE | AMOUNT |
|---|---|---|---|
| *Bowmaker, James Keith, Ph.D.<br>University of California<br>Los Angeles, California | Dr. Frederick Crescitelli | Visual pigments and the biochemical aspects of the visual process | $6,600 |
| Clarkson, John G., M.D.<br>University of Miami<br>Bascom Palmer Eye Institute<br>Miami, Florida | Donald M. Gass, M.D. | Effects of photocoagulation treatment on the course of diabetic retinopathy | 7,500 |
| Fineberg, Edward M., M.D.<br>University of Miami<br>Bascom Palmer Eye Institute<br>Miami, Florida | Dr. Robert Machemer | Experimental study of the origin of massive preretinal retraction (MPR) | 7,500 |
| *Manalaysay, Alvin, Ph.D.<br>California Institute of Technology<br>Pasadena, California | Dr. Walter A. Schroeder | Determination of the primary structure of crystallin | 3,600 |
| Matsuda, Hidehiko, M.D.<br>Columbia University<br>New York, New York | George K. Smelser, Ph.D. | Electron microscopic study on alkali-burned cornea | 7,500 |
| Miles, Frederick A., Ph.D.<br>National Institute of<br>Mental Health<br>Bethesda, Maryland | Edward V. Evarts, M.D. | Role of the cerebellum in initiation and control of eye movements in the monkey | 3,000 |
| *Morrison, Dennis R., Ph.D.<br>University of Florida<br>Gainesville, Florida | Herbert E. Kaufman, M.D. | Normal and pathological corneal physiology: Effects of external semipermeable membranes and related chemotherapeutic applications | 2,000 |
| *Uga, Shigekazu, Ph.D.<br>Columbia University<br>New York, New York | George K. Smelser, Ph.D. | Structure and pathology of the optic nerve head and of Müllerian cells | 7,500 |
| Van de Kamp, Maarten J. L., Ph.D.<br>Children's Hospital Medical Center<br>Boston, Massachusetts | Johan Zwaan, M.D. | Detection and characterization of lens proteins during eye development in normal and mutant mice | 7,500 |
| Weinstein, David B., Ph.D.<br>University of Pennsylvania<br>Philadelphia, Pennsylvania | Herbert A. Blough, M.D. | Lipid metabolism in cells affected with viruses which cause ophthalmic disease | 7,500 |

* Continuation award.

## GRANTS-IN-AID

| NAME AND INSTITUTION | DIRECT SUPERVISOR | PROJECT TITLE | AMOUNT |
|---|---|---|---|
| Ziemianski, Matthew C., M.D.<br>University of California<br>San Francisco, California | Wm. H. Spencer, M.D. | Light and scanning electron microscopic observations of bacterial conjunctival cellular interaction | 7,500 |

## STUDENT FELLOWSHIPS

| NAME AND INSTITUTION | DIRECT SUPERVISOR | PROJECT TITLE | AMOUNT |
|---|---|---|---|
| Bundy, Walter E.<br>Department of Ophthalmology<br>Virginia Commonwealth University<br>Richmond, Virginia | Walter J. Geeraets, M.D. | The effect of vitamin A on the healing of experimental corneal lesions | $600 |
| Ching, Wei-Mei<br>Division of Natural Science II<br>University of California<br>Santa Cruz, California<br>(Burroughs Wellcome Co. fund) | Dr. Edward Dratz | Structure and function of the visual membrane | 750 |
| Eichenbaum, Joseph<br>Department of Ophthalmology<br>Bascom Palmer Eye Institute<br>University of Miami<br>Miami, Florida<br>(Abraham Silver Memorial Fund) | Duco I. Hamasaki, Ph.D. | Response of normal and visually deprived neurons of cats to moving stimuli | 600 |
| Finger, Stephen<br>Department of Ophthalmology<br>Columbia University<br>New York, New York<br>(Burroughs Wellcome Co. fund) | Emil Wirostko, M.D. | Is there an infectious agent in the etiology of diabetic retinopathy? | 600 |
| Franklin, Laurence K.<br>Division of Natural Science II<br>University of California<br>Santa Cruz, California<br>(James Thurber memorial fund) | Dr. Edward Dratz | The mechanism of visual excitation | 750 |
| Goodman, Robert P.<br>Department of Biochemistry<br>Virginia Commonwealth University<br>Richmond, Virginia<br>(Burroughs Wellcome Co. fund) | Dr. James M. Collins | Alteration of DNA during lens cell differentiation | 875 |
| Johnson, Susan Bagley<br>The Marine Biological Laboratory<br>Woods Hole, Massachusetts | Seymour Zigman, Ph.D. | Near ultraviolet effects on visual cell biochemistry | 750 |
| Murphy, Charles L.<br>Department of Biochemistry<br>University of Georgia<br>Athens, Georgia<br>(William N. Creasy fund) | Dr. John Lee | Photoenzymes | 750 |

## CLINICAL RESEARCH SERVICE PROJECTS

Fight for Sight Children's Eye Clinic, Columbia-Presbyterian Medical Center, New York, Philip Knapp, M.D., Director (established 1961) ..... $18,000

Fight for Sight Children's Eye Clinic, New Jersey College of Medicine and Dentistry, Newark, New Jersey, (initial award). Paul T. McAlpine, M.D., and Walter T. Rados, M.D., Acting Directors 15,000

Fight for Sight Children's Eye Clinic, Eye and Ear Hospital of Pittsburgh, Pennsylvania, David A. Hiles, M.D., Director (established 1967) ..... 17,000

Fight for Sight Children's Eye Clinic, Wills Eye Hospital, Philadelphia, Pennsylvania, Robison, D. Harley, M.D., Director (established 1964) ..... 17,500

### Special award

Travel grant to Almen L. Barron, Ph.D. of State University of New York at Buffalo to help defray transportation costs for a visiting professorship at Hebrew University, Jerusalem, Israel, for study of the immunologic aspects of trachoma and training in electron microscopy .....$920

## Personals

### Gerald L. Portney

Gerald L. Portney was appointed chairman of the Department of Ophthalmology in the School of Medicine at the University of California, Davis.

Before coming to Davis, Dr. Portney was an assistant professor of ophthalmology and director of the Glaucoma Service at Stanford University Medical Center in Palo Alto, California.

Dr. Portney received his M.D. degree from Northwestern University in 1962. He interned at Cook County Hospital and trained in ophthalmology at the University of Illinois Eye and Ear Infirmary. He served as clinical ophthalmologist on the Navajo Indian Reservation and then as medical research officer and ophthalmologist on the Papago Indian Reservation with the US Public Health Service.

He was an NIH Special Fellow at the University of Michigan where he received a M.A. in mathematics.

### R. Townley Paton

R. Townley Paton, Southampton, Long Island, received the Lighthouse award for distinguished service in recognition of his contribution to the field of blindness, toward the advancement of keratoplasty, and as a founder of the Eye Bank for Sight Restoration, and his services to this cause in New York City and across the nation.

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## INSTRUCTIONS FOR SUBMITTING NEWS ITEMS

Each news item intended for publication in the American Journal of Ophthalmology must be submitted in typewritten form. Each news item must be submitted on a separate sheet of 8½ × 11 heavy bond paper, the typing should be double-spaced, and each item should be written in narrative style; names, titles, and offices should not be listed separately, but included in the body of the announcement.

News items should include full information regarding the event publicized (who, what, when, where, and occasionally, why), and should provide the name and address of the person responsible for the accuracy of the item. All news items must be submitted *four months in advance of publication,* and should be mailed directly to the office of the News Editor: Thomas Chalkley, M.D., 700 North Michigan Avenue, Chicago, Illinois 60611.

## THE BASIC SCIENCE COURSE IN OPHTHALMOLOGY

UNIVERSITY OF PENNSYLVANIA
SCHOOL OF MEDICINE
OFFICE OF GRADUATE MEDICAL EDUCATION
July 10, 1972 through October 28, 1972

The sixteen week basic science course in ophthalmology is especially designed to give medical graduates entering their residency training in ophthalmology an excellent basic foundation for their work. Instruction is by lecture, demonstrations, laboratory work, conference and practice clinics. Full use is made of the University's facilities. The program is under the organization and supervision of Dr. Harold G. Scheie, Professor and Chairman of the Department of Ophthalmology. The faculty is composed of members of the basic science and clinical departments of the University of Pennsylvania School of Medicine supplemented by the following guest lecturers:

Boeder, Paul Antonkurt, Ph.D.
Donaldson, David D., M.D.
Dowling, John, Ph.D.
Ellis, Philip P., M.D.
Falls, Harold F., M.D.
Fine, Ben S., M.D.
Forster, H. Walter, Jr., M.D.
Frayer, William C., M.D.
Friedman, Ephraim, M.D.
Gass, J. Donald, M.D.
Haas, Joseph S., M.D.
Hallett, Joseph W., M.D.
Harris, John E., Ph.D., M.D.
Hoover, Richard E., M.D.
Johnson, Robert J., M.D.
Kinsey, Everett V., M.D.
Koelle, George B., Ph.D., M.D.
Krill, Alex E., M.D.
Kurz, George H., M.D.
Lambertsen, Christian J., M.D.
Lemoine, Albert N., M.D.
Linksz, Arthur L., M.D.
Rose, Edward, M.D.
Stone, Hrant H., M.D.

Subjects include: anatomy, principles of anesthesia, bacteriology, biochemistry, biomicroscopy, blind patient care, cryosurgery, electron microscopy, embryology, fundamentals of glaucoma and gonioscopy, genetics, immunology and tissue transplantation, light coagulation, microbiology, neuroophthalmology, ocular motility, ocular photography, optics, pathology, perimetry, pharmacology-physiology, principles of laser energy, refraction, roentgenology, statistics, principles of tonometry and tonography, ultrasound in ophthalmology and current concepts of uveitis.

To enroll in this program physicians must return a completed application. Students will not be accepted for isolated portions of the course and a certificate is awarded upon completion. Tuition for the course is $575.00. The American Board of Ophthalmology has indicated that the time spent in this course is acceptable as credit.

Applications should be made promptly. Persons wishing further information should write to:

THE DIRECTOR
OFFICE OF GRADUATE MEDICAL EDUCATION
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## THE RETINA SERVICE WILLS EYE HOSPITAL
### PHILADELPHIA, PENNSYLVANIA

Announces a Course on
**MACULAR DISEASES**

To be held at the Philadelphia County Medical Society Building, Philadelphia, Pennsylvania

March 10 and 11, 1972

Faculty for the course will include:

William H. Annesley, M.D.
Harold Cross, Ph.D., M.D.
Jay Federman, M.D.
Richard Goldberg, M.D.
Alfred Lucier, M.D.
P. R. McDonald, M.D.
Charles J. Rife, M.D.
Merlyn Rodriguez, M.D.
L. K. Sarin, M.D.
George Spaeth, M.D.
William Tasman, M.D.
A. Zimmermann, M.D.

The course will cover the clinical fluorescein and pathologic aspects of heritable macular disorders, choroidal diseases causing detachment of the retina and pigment epithelium, serous detachment of the retina secondary to hypertensive and collagen diseases, macular dysfunction secondary to vitreous abnormality, retinal inflammatory and toxic disease affecting the macula, macular dysfunction secondary to trauma, tumors of the posterior pole and the sphingolipidoses.

Tuition will be $100. Special rate of $40 available for residents upon application from their Department Head. Checks should be made payable to Retina Service, Wills Eye Hospital and mailed to William Tasman, M.D., Retina Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pa. 19130.



Louisiana State University School of Medicine
Department of Ophthalmology and
The Eye Foundation of America

# SYMPOSIUM ON STRABISMUS

WITH EMPHASIS ON NEURO-OPHTHALMOLOGICAL ASPECTS

Friday and Saturday, March 3 and 4, 1972

TOPICS

Indications and contraindications for: combined vertical and horizontal muscles surgery, multiple horizontal muscle surgery, recess-resect operations, bilateral resection operations, bilateral recession operations; strabismus and reading problems; dyslexia; the forced traction test; diagnosis of superior oblique palsy; management of superior oblique palsy; management of complete paralysis of ocular muscles; NRC-ARC—what is its place in diagnosis and prognosis?; the management of congenital esotropia; intentional vs. unintentional overcorrections in eso deviations; intentional vs. unintentional overcorrections in exo deviations; prisms in the management of strabismus; the present status of miotics versus bifocals; refractive errors in strabismus management; comparative methods for assessing rotation defects; management of endocrine-eye muscle problems; management of adult acquired strabismus.

Write to George M. Haik, M.D., Professor and Head,
Department of Ophthalmology, L.S.U. Medical Center,
1542 Tulane Avenue, New Orleans, Louisiana 70112.

## STANFORD BASIC SCIENCE COURSE IN OPHTHALMOLOGY

**July 5 through September 8, 1972**

**Stanford University Medical Center, Stanford, California**

For residents and prospective residents—approximately 290 hours of instruction with a faculty of forty-five.

Sections include:

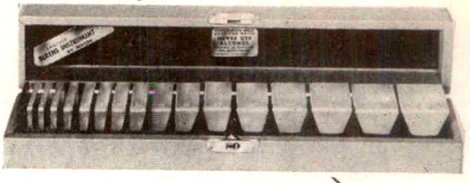
1. Anatomy (25½ hours)
2. Microbiology and Immunology (39 hours)
3. Pathology (69 hours)
4. Physiology (39 hours)
5. Neuro-ophthalmology and Neuroanatomy (33 hours)
6. Optics and Theory of Refraction (33 hours)
7. Embryology and Genetics (9 hours)
8. Motility (30 hours)
9. Biochemistry (9 hours)
10. Pharmacology and Toxicology (29 hours)

Some of the lecturers are as follows: Crowell Beard, Raynold Berke, Paul Boeder, Brooks Crawford, Phil Ellis, William Green, Arthur Jampolsky, Alan Scott, Robert Shaffer, Richard Sogg, William Spencer, Phillips Thygeson.

Tuition $575.00. For further information and application forms please write to J. W. Bettman, M.D., Division of Ophthalmology, A230, Stanford Medical Center, Stanford, California 94305.

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REGISTRATION: $100—Payable to Massachusetts Eye and Ear Infirmary
REGISTRAR: Charles Regan, MD, 243 Charles Street, Boston, MA 02114

The First International Surgical Eye Symposium in Ophthalmology will be held in Bologna, Italy on April 23, 1972. The format of the program is rather unusual and should prove to be a most exciting one. Outstanding and renowned surgeons will perform live surgery on patients to demonstrate a variety of techniques in cataract, glaucoma, cornea and plastic eye surgery. Ancillary subjects related to ophthalmic surgery will be presented by a roster of outstanding ophthalmologists. Operative sessions will be televised and simultaneous translations will be held in Italian, English and French. For further details contact:

Prof. G. Cristini, President
Clinica Oculistica Universita
Via Massarenti #9
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The Bascom Palmer Eye Institute
Department of Ophthalmology of the
University of Miami School of Medicine
and the Florida Lions Eye Bank at Miami
Announces a Symposium on

# OPHTHALMIC PLASTIC AND CORNEAL SURGERY

To be held at the Diplomat Hotel,
Miami Beach (Hollywood), Florida

March 26-31, 1972

Faculty for the course will include:

| | |
|---|---|
| Dr. Crowell Beard | Dr. J. H. King |
| Dr. Jorge Buxton | Dr. James Major |
| Dr. Ramon Castroviejo | Dr. A. E. Maumenee |
| Dr. Claes Dohlman | Dr. Gordon Miller |
| Dr. Max Fine | Dr. Edward W. D. Norton |
| Dr. Richard Forster | Dr. Frank Polack |
| Dr. J. Donald M. Gass | Dr. Marvin Quickert |
| Dr. Russell Harner | Dr. Norman Sanders |
| Dr. Danny Jones | Dr. Byron Smith |
| Dr. A. Dalma Kende | Dr. David Soll |

Dr. Richard Tenzel

This symposium will cover the corneal and ophthalmic plastic field. Multiple lectures will be given with ample time for panel discussion and questions from the registrants.

Afternoons will be set aside for recreation including tennis and golf tournaments. There will be planned entertainment for most evenings.

Tuition will be $175, breakfasts included. Special rate of $75 available for residents upon application from their Department Head. Checks should be made payable to "Bascom Palmer Eye Institute" and mailed to Ophthalmic Plastic and Corneal Surgery Symposium, Bascom Palmer Eye Institute, P.O. Box 875, Biscayne Annex, Miami, Florida 33152.

## Announcement of
## TWELFTH ANNUAL INSTRUCTIONAL COURSE IN CONTACT LENS FITTING BY THE OPHTHALMOLOGIST

**April 8-9, 1972**

Sponsored by
The Rudolph Ellender Medical
Foundation, Inc.

Co-ordinated with the
New Orleans Academy of Ophthalmologist's
Meeting on "Contact Lenses"
April 9-14, 1972

PLACE

Roosevelt Hotel, New Orleans, La.

TUITION

$85.00 ($40.00 Out of State Residents and M.D.'s Technicians)

PANEL MEMBERS

Colonel Budd Appleton, M.D., Walter Reed Hostp., Washing. D.C.
Jos. A. Baldone, M.D., New Orleans, Louisiana
Antonio R. Gassett, M.D., Gainesville, Florida
Herbert L. Gould, M.D., White Plains, New York
G. Peter Halberg, M.D., New York, New York
Jack Hartstein, M.D., St. Louis, Missouri
Frank Hoefle, M.D., New York, New York
Whitney G. Sampson, M.D., Houston, Texas
Keith Whitham, Buffalo, New York

TOPICS

Practical technics of fitting of hard and soft gel lenses will be actually demonstrated, audience participation in handling of lenses.

Full description of the Series System (Inventory System) fitting technic of hard lenses.

Didactic lectures will be held to a minimum (in co-operation with the New Orleans Academy's Program which follows).

WORKSHOP

For M.D.'s Technicians in evening

LADIES DAY

Saturday, April 8, 1972 with planned activities.

## INDIRECT OPHTHALMOSCOPY OF THE PERIPHERAL RETINA

Purpose: To teach this new technique—the normal anatomy of the peripheral retina to residents and ophthalmologists.

Contents: Demonstrates and discusses normal anatomy of the equatorial and oral region of the retina as viewed during indirect ophthalmoscopy and scleral indentation. All normal anatomy and variations are discussed, and presented in views of post mortem eyes and shown in scenes taken with the Stenstrom cine. This technique demonstrates the actual views of the fundus as seen during clinical examinations.

Running Time: 41 minutes—16 mm sound

Cost: Rental $25.00 per week
Purchase price $300.00

For information contact: Retinal Service
Department of Ophthalmology
University of Iowa College of Medicine
Iowa City, Iowa 52240

## NATIONAL SPRING MEETING
THE AT
*Greenbrier*
April 26-29, 1972

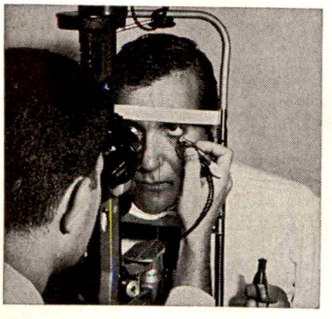
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Louis J. Girard, M.D., Houston, Tx.
Frank W. Newell, M.D., Chicago, Ill.
John T. Simonton, M.D., New York, N.Y.
Frederick Stocker, M.D., Durham, N.C.

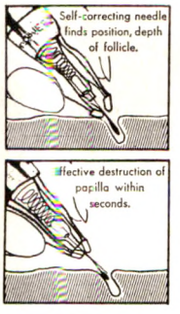
*Otolaryngology Speakers*
Phillip Anthony, M.D., Fort Worth, Tx.
William R. Hudson, M.D., Durham, N.C.
Jerrie Cherry, M.D., Nashville, Tenn.
James R. Leonard, M.D., Philadelphia, Pa.

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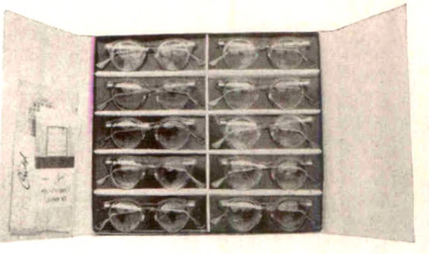
1. Mishima, S. and D. M. Maurice, The Effect of Normal Evaporation on the Eye, Exp. Eye Res., 7:46, 1961.
2. Bahr, Gunnar, Measurement of the Effect of Solutions of Different Osmotic Pressure on the Thickness of the Living Cornea, Trans. of Ophthal. Soc. U.K., *68*:515, 1949.

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# Apollo Space Flight Veteran: Methulose, for dry eyes!

Methulose artificial tears lubricate sensitive ocular tissues to provide comfortable, soothing relief from eye dryness and irritation without blurring vision. Little wonder it is a big item on Apollo flights where dry eyes could present serious problems.

Meanwhile, back on earth, Methulose might be the simple solution to the dry-eye problems of many of your patients. A non-irritating buffered aqueous solution containing Methylcellulose U.S.P. preserved with Benzalkonium Chloride 1:25,000, it is available in 15cc and 30cc direct application plastic containers. Write for a generous supply of 5cc starter samples.

**PROFESSIONAL PHARMACAL CO., INC.**

P. O. Box 230 300 W. Josephine St., San Antonio, Texas 78206



## There's no biting sting with "comfort strength" Epifrin ½%, 1%

Epifrin® (l-epinephrine) has long offered the most economical, convenient l-epinephrine available to glaucoma patients. Now, with "comfort strength" Epifrin ½% and 1%, the biting sting is gone too! Evaluate our "comfort strengths" with your glaucoma patients. Have them compare the comfort of EPIFRIN ½% with any other l-epinephrine. You'll find there is no significant difference in patient acceptance. There is growing documentation of the efficacy of these lower concentrations. (1, 2) Lower concentrations also mean reduced side effects and no blurring or impaired vision. Now the economy and convenience of "comfort strength" Epifrin® ½% and 1% make a lot more sense.

**References:** 1. Kronfeld, P.C.: Invest. Ophth. 3258 (June) 1964. 2. Harris, L. S.; Galin, M.A.; and Lerner, R.: Annals of Oph. 219 (June) 1970. **Prescribing Information:** Contains: levo-epinephrine (as the HC1)...2%, 1%, ½%, with: benzalkonium chloride, sodium metabisulfite, disodium edetate, and purified water. **Indications:** Chronic simple glaucoma. **Contraindications:** Should not be used in patients who have had an attack of narrow angle glaucoma since dilation of the pupil may trigger an acute attack. **Warnings:** Undesirable side reactions may include: eye pain or ache, browache, headache, conjunctival hyperemia, and allergic lid reactions. Adrenachrome deposits in the conjunctiva and cornea after prolonged epinephrine therapy have been reported. Epinephrine has been reported to produce macular edema in some aphakic patients. **Precautions:** Should be used with caution in patients with a narrow angle since dilation of the pupil may trigger an acute attack of glaucoma. **Dosage:** The usual dosage is one drop in the affected eye(s) once or twice daily. However, the dosage should be adjusted to meet the needs of the individual patient. **Note:** Protect from excessive light and heat. If the solution discolors or a precipitate forms it should be discarded. **How Supplied:** 0.5% and 1.0% strengths in 15 cc plastic dropper bottles. 2% in 5 cc and 15 cc plastic dropper bottles. On prescription only.

**Epifrin** (l-epinephrine)

ALLERGAN Irvine, Calif./Montreal, Canada